

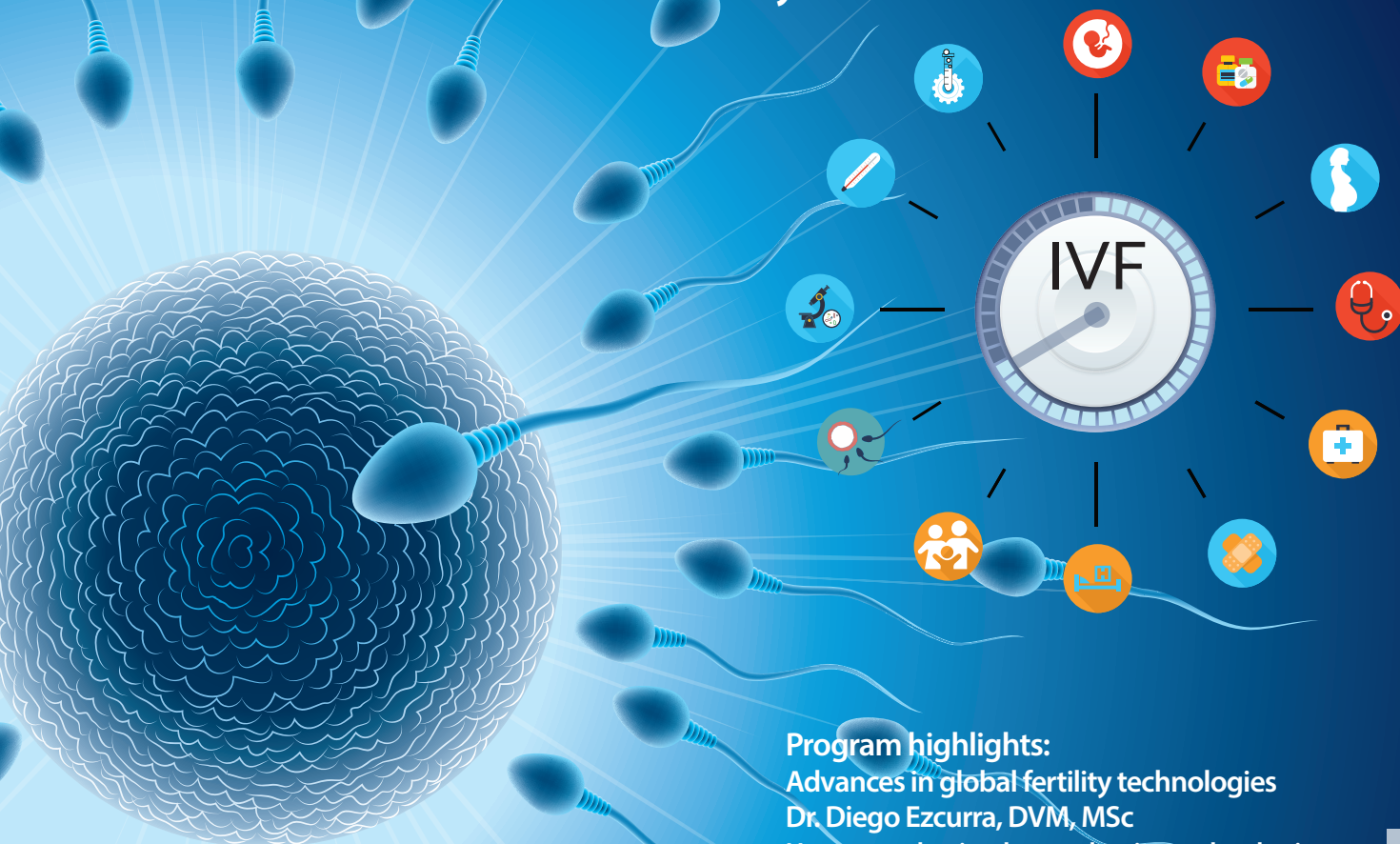
TBILISI, GEORGIA

MEDICAL TIMES

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MAGAZINE №4

**Symposium and Workshop of the 20th World Congress on Human Reproduction:
"Infertility 35+"**



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Prof. Nino Museridze, MD, PhD

– President, Georgian Association of Oncofertility, Georgia

Prof. Archil Khomasuridze, MD, PhD

– President of Georgian Association of Reproductive Health, Georgia

Andrea Genazzani, MD, PhD, DSc (Honoris Causa)

– Emeritus Professor, University of Pisa, Italy;
President of IAHR.

Program highlights:

Advances in global fertility technologies

Dr. Diego Ezcurra, DVM, MSc

Human and animal reproductive technologies.
DVM (UBA); Fellowship (UC Davis); MSc (EVMS).

Fertility preservation

in women with Turner syndrome

Prof. Yossi Mizrachi

**Director, Fertility Unit,
Edith Wolfson Medical Center, Holon, Israel;
affiliated with Tel Aviv University, Israel.**

Fresh vs frozen: when and for whom?

Prof. Raoul Orvieto, MD

MMSc, Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Israel.

Varicocele and DNA fragmentation: evaluation of a new automated test versus the TUNEL test

Gian Maria Busetto, MD, PhD

**Associate Professor of Urology,
University of Foggia, Italy; Senior Urologist,
University Hospital “Ospedali Riuniti” of Foggia.**

MEDICAL TIMES

SPECIAL EDITION

20th World Congress on Human
Reproduction Symposium and
Workshop: “Infertility 35+”

* * *

Supplement to the Abstract Book
of the 20th World Congress on Human
Reproduction Symposium
and Workshop: “Infertility 35+”

№4

Tbilisi, Georgia
2025

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Georgian-German Reproduction Center, Georgia

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SYMPOSIUM AND WORKSHOP OF THE 20TH WORLD CONGRESS ON HUMAN REPRODUCTION "INFERTILITY 35+" SUPPORTING COMPANIES



CONTENTS

ABSTRACT BOOK

20th World Congress on Human Reproduction Symposium and Workshop: “Infertility 35+”

- 24** **Nino Abesadze**
Jenaro Kristesashvili
Vitamin D in Fertile Women With Endometriosis
- 26** **Ana Aivazova**
Silent inhabitants: Exploring the role of the endometrial microbiome in implantation failure and ART success
- 28** **Suleyman Aktuna**
Enhancing PGT-A success and minimizing bias:
The promise of a premium approach
- 29** **Evrin Ünsal**
Enhancing Genetic Diagnosis and Aneuploidy Screening
in PGT-M Cycles for Improved Clinical Outcomes
- 32** **Volkan Baltaci**
From IVF to genetics: Enhancing IVF laboratory monitoring and safety
- 33** **Tamar Barbakadze**
Jenaro Kristesashvili
Mariam Shervashidze
Thea Pataraia
Tamar Kbilashvili
Mariam Gabadze
Temiko Zhorzholadze
Nino Kutchukhidze
Nina Kim
Lia Chkonia
Role of endometrial receptivity analysis
in enhancing ART outcomes for advanced-age patients
- 35** **Ido Ben-Ami**
GnRH antagonists vs. progestin-primed ovarian stimulation (PPOS):
Is it time to change protocols?
- 36** **David H. McCulloh**
Caroline McCaffrey
James A. Grifo
Frozen euploid single embryo transfer:
Factors from retrieval and fet cycles that influence live birth outcomes

CONTENTS

- 38** **Tatiana Nazarenko**
Possibilities for improving IVF outcomes in women with unexplained infertility and diminished ovarian reserve
- 42** **Raoul Orvieto**
Fresh versus frozen, when and to whom?
- 43** **Viktoriia Yuzko**
Tamara a. Yuzko
Oleksandr Sambolskyi
OptiPredict IVF: An AI-powered platform for personalized controlled ovarian stimulation – Experience from a Ukrainian clinic
- 45** **Asymbekova G. U.**
Abekov K. D.
Asymbekova A. Sh.
Ibraimova R. N.
Chinaliev I. S.
Long-term Outcomes for Children Following Intrapartum Complications: Analysis of Leading Risk Factors in High-Risk Women, Including Those Undergoing IVF
- 47** **Tamar Antelava**
Critical analysis of antenatal care in singleton IVF pregnancies in Georgia: Polypharmacy, iatrogenic complications, and quality assessment
- 48** **Elene Asanidze**
Zurab R. Tsetskhladze
Jenaro Kristesashvili
Manana Urjumelashvili
Malkhaz Vakhania
Genetic and metabolic impact in PCOS: MTHFR polymorphisms, homocysteine, insulin resistance, and pregnancy outcome
- 50** **Manana Gegechkori**
Ovarian endometriosis: The need for personalized management
- 51** **Lali Pkhaladze**
Nana Chopikashvili
Reasonable and rational therapy of menstrual disorders

CONTENTS

- 53** | Lali Pkhaladze
Nino Davidova
Nino Datoshvili
Thin endometrium: Potential of enzyme-based therapy
- 55** | George Tevdorashvili
Mariami Andguladze
Hormonal correction of menstrual cycle disorders (MCD):
Focus on sex steroids
- 57** | George Tevdorashvili
Mariami Andguladze
The hormonal triangle of polycystic ovary syndrome (PCOS):
From neuroendocrine factors to metabolic disorders and infertility
- 60** | David Skhirtladze
Jenaro Kristesashvili
Ramaz Charekishvili
Efficacy of combined surgical and hormonal therapy for infertile
patients with deep endometriosis
- 61** | Manana Urjumelashvili
Jenaro Kristesashvili
Eka Asanidze
Homocysteine levels in patients with polycystic ovary syndrome
(PCOS) with and without insulin resistance
- 62** | Shorena Tchiokadze
Elene Asanidze
Jenaro Kristesashvili
Insulin resistance and hyperhomocysteinemia as risk factors
for recurrent pregnancy loss in polycystic ovary syndrome
- 64** | Marika Japaridze
Effect of intraoperative lidocaine injection on postoperative pain and
recovery in endometrial cancer patients undergoing laparoscopically
assisted vaginal hysterectomy with ICG SLN mapping
- 66** | Nutsa Chighladze
Follicular variant of papillary thyroid microcarcinoma arising
in struma ovarii: A rare case report

CONTENTS

- 68 Nino Dzelashvili
Microwave ablation of uterine fibroids
- 69 Irakli Simonia
Jenaro Kristesashvili
Marika Japaridze
Davit Skhirtladze
Postoperative management of hysteroscopic metroplasty
for patients with septate and T-shaped uterus
- 71 Zaza Tsitsishvili
Fertility-sparing management in early-stage endometrial cancer:
Patient selection and oncologic considerations
- 74 Mariam Chipashvili
Genetic aspects of male infertility
- 76 Mariam Chipashvili
Maka Jorbenadze
Sopo Kvaliashvili
Jenaro Kristesashvili
Nana Kurashvili
Reproductive genetic advances: Solutions or new challenges?
- 77 Tamar Didbaridze
Shorena Tchiokadze
Maia Janelidze
Ivliane Surmava
Bachana Aptsiauri
Prevalence and distribution of high-risk HPV genotypes among
women with cytological abnormalities in Georgia
- 78 Ana Jibladze
Jenaro Kristesashvili
Elene Asanidze
Tetrasomy X in an adolescent girl
- 79 Tea Khurodze
Vitali Vashakidze
Sopo Javelidze
Basa Gegeshidze
Ana Pruidze
Rare case of concomitant pseudohypoparathyroidism
and bilateral ovarian teratoma

CONTENTS

- 80** | **Nino Ustiashvili**
Mariam Garibashvili
The immunology of endometriosis: how immunological knowledge is shaping management strategies
- 82** | **Jenaro Kristesashvili**
Mariam Chipashvili
Maka Jorbenadze
Elene Asanidze
Nino Sigua
X chromosome anomalies as a cause of non-iatrogenic premature ovarian insufficiency
- 84** | **Evrin Ünsal**
Optimizing donor carrier screening: strategies for effective matching
- 86** | **Mariami Andguladze**
George Tevdorashvili
Effects of oral dehydroepiandrosterone (DHEA) supplementation on hormonal profile, menopausal clinical symptoms, and sexual function in early postmenopausal symptomatic Caucasian women
- 88** | **Martin Birkhaeuser**
When should hormone replacement therapy be continued after the age of 60 years?
- 90** | **Martin Birkhaeuser**
Hormonal contraception: Effect on peak bone mass
- 92** | **Alfred O. Mueck**
Choice of the progestogen for MHT in menopausal women
- 94** | **Alfred O. Mueck**
Xiangyan Ruan
Breast cancer caused by MHT:
The two main mechanisms and how to reduce the risk
- 96** | **Natavan Akhundova**
Features of hormonal changes in women of reproductive age with hyperandrogenism syndrome

CONTENTS

- 98** **Sophio Kvaliashvili**
Jenaro Kristesashvili
Mariam Chipashvili
Maka Jorbenadze
Nino Kurashvili
Diagnosis and management of pregnancy in a patient with nonclassic congenital adrenal hyperplasia (nccah) and recurrent pregnancy loss (rpl)
- 100** **Lali Gogia**
Early diagnosis of risk factors for preeclampsia during the initial stage of pregnancy
- 102** **Vakhtang Gurabanidze**
Tinat Gagua
The impact of maternal obesity on pregnancy outcomes: A cross-sectional cohort study
- 104** **Revaz Sulukhia**
Larisa Melia
Aleksander Sulukhia
Nino Davidova
The efficacy of pessary in preterm birth prevention in multifetal pregnancies
- 105** **Lana Ezieshvili**
Natia Pkhaladze
Sophia Tamazashvili
Spontaneous heterotopic pregnancy: A rare diagnostic challenge in early gestation
- 106** **Dina Kurdiani**
Nino Sharikadze
Irakli Zhvania
Cervical cancer in pregnancy
- 110** **Maia Janelidze**
Tamar Matitashvili
Shorena Tchiokadze
Pregnancy complications in congenital hypofibrinogenemia associated with MTHFR (C677T) genotype: A report of two cases
- 111** **Ana Ghviniashvili**
Mariam Kharaishvili
The impact of post-cesarean section isthmocele on reproductive health

CONTENTS

- 113** | **Ia Chapidze**
Jenaro Kristesashvili
Diagnostic capabilities for müllerian anomalies
in women with reproductive disorders
- 114** | **Guranda Okropiridze**
Arsen Gvenetadze
Revaz Sulukhia
Rusudan Gvenetadze
Rusudan Impact of the first-trimester preeclampsia screening test
on the outcome of pregnancy
- 116** | **Mariami Andguladze**
George Tevdorashvili
The role of GABAergic dysregulation in PCOS and FHA:
Shared neuroendocrine pathways and divergent clinical manifestations
- 117** | **Shota Janjghava**
Elene Giorgadze
Nino Sikharulidze
Revazi Jamburia
Endocrine-metabolic panel in pubertal development disorders
- 118** | **Rusudan Jashi**
The role of the vegetative nervous system in the development
of reproductive function disorders in children of mothers treated
for polycystic ovary syndrome
- 120** | **Rusudan Jashi**
Maternal medication and neonatal risk: The case for digital integration
- 121** | **Blazej Meczekalski**
Neuroendocrine background of functional hypothalamic
amenorrhea (FHA)
- 123** | **Blazej Meczekalski**
PCOS in adolescents: Current view
- 124** | **Archil Khomasuridze**
Marina Jangidze
New approaches to the management of pregnant women
with antiphospholipid syndrome (APS) and genetic thrombophilia
against the background of myeloproliferative diseases (MPD)

CONTENTS

- 125 Mariam Ramishvili
Elisabed Pkhaladze
Nino Davidova
Lali Pkhaladze
Bardet-Biedl syndrome presenting with abnormal uterine bleeding:
A case report
- 126 Natalia Rusakova
Irina Gogokhia
Tamar Diakonidze
The effect of immunotherapy in reproductive medicine
- 127 Salome Sabulua
Hormonal interference: Unveiling the adolescent spectrum
of hyperprolactinemia
- 130 Ketevan Shengelaia
Androgen receptor expression in ovarian and breast epithelial
cancers and its association with proliferation, apoptosis,
and cancer stem cell features
- 131 Ramaz Charekishvili
David Skhirtladze
Ia Shiukashvili
Uterine reconstruction following near-complete transection during
myomectomy: Implications for congenital repair
- 132 Ana Ghviniashvili
Nata Nakaidze
Salome Sabulua
Nana Chopikashvili
From prenatal diagnosis to postnatal surgery:
A case of giant fetal ovarian cyst requiring neonatal intervention
- 134 Lilit Kalashyan
Artur Sarkisov
The use of hyaluronic acid gel to prevent intrauterine adhesion
after intrauterine operations
- 136 Manana Mgaloblishvili
Anton Mgaloblishvili
Nino Vardosanidze
Nata Nakaidze
Reconstruction of the fallopian tube using office mini-hysteroscopy
during infertility treatment

CONTENTS

- 137** **Natia Pkhaladze**
 Lana Ezieshvili
 Sophia Tamazashvili

 Latent complications following conservative myomectomy
 in an IVF patient – A case presentation
- 139** **Natia Pkhaladze**
 Lana Ezieshvili
 Sopho Tamazashvili

 Fetal edema in IVF pregnancy – Antenatal diagnosis
 and management: A case report
- 140** **Gunay Sultanova**

 A successful IVF procedure in a woman with a unicornuate uterus:
 Our clinical experience
- 142** **Tevfik Yoldemir**

 ART Outcomes in Women with Endometriosis and Adenomyosis
- 144** **Ariel Hourvitz**

 Implementation of artificial intelligence (AI)
 in assisted reproductive technology
- 146** **Johannes Bitzer**

 Contraception in patients with psychiatric disorders
- 147** **Johannes Bitzer**

 How to understand the adolescent brain
- 148** **Ekaterine Tchanturia**
 Ketevan Shengelaia

 When PMS affects the mind: SSRIs as a path to emotional stability
- 150** **Mari Malazonia**

 Nutrition, reproduction, and age
- 152** **Maka Jorbenadze**
 Mariam Chipashvili
 Sophio Kvaliashvili
 Jenaro Kristesashvili
 Nino Kurashvili

 Reproductive health characteristics of adolescent girls in Georgia

CONTENTS

- 154 Ahmad Karimov
Khaitboeva F. A.
Determination of depression level using the Beck Depression Inventory in women after medical abortion
- 156 Apolon Karseladze
The role of ischemia in cervical carcinogenesis
- 158 Frank A. Chervenak
Amos Grunebaum
Reproductive healthcare at risk:
The ethical response to zealotry and inequity
- 159 Frank A. Chervenak
Amos Grunebaum
Obstetric violence is a misnomer:
Reframing the discourse on mistreatment in maternity care
- 160 Camil Castelo-Branco
Endocrine disruptors: The need of common sense
- 162 Wolfgang Holzgreve
Stem cells in obstetrics and prenatal medicine
- 164 Wolfgang Holzgreve
Update on non-invasive prenatal testing:
How did NIPT change the practice of prenatal diagnosis?
- 165 Wolfgang Holzgreve
Infertility after 40: A challenge for modern reproductive medicine
- 166 Vyacheslav Lokshin
Unsolved issues of modern reproductive medicine
- 168 Teimuraz Gagnidze
Sperm DNA fragmentation in male partners of couples with unexplained infertility and recurrent pregnancy loss in Georgia
- 169 Beka Sibashvili
Shalva Chovelidze
Tengiz Zhorzholadze
Nino Kutchukhidze
Ekaterina Volkomorova
Lia Chkonia
Micro-TESE: The leading surgical solution for severe non-obstructive azoospermia

CONTENTS

- 172** | **Temiko Zhorzholadze**
Nino Kutchukhidze
Ekaterina Volkomorova
Beka Sibashvili
Mariam Shervashidze
Thea Pataraia
Tamar Barbakadze
Tamar Kbilashvili
Mariam Gabadze
Lia Chkonia
Comparison of two sperm processing methods and their impact on fertilization, embryogenesis, and euploidy rates
- 174** | **Ludmila Barbakadze**
Natalia Khonelidze
Gia Tsagareishvili
Fertility preservation: Current trends, challenges, and opportunities
- 176** | **Yossi Mizrahi**
Fertility preservation in women with Turner syndrome
- 177** | **Sholpan Karibayeva**
Oocyte cryopreservation as a life strategy:
Clinical outcomes and patient emotions
- 180** | **George Tevdorashvili**
The latest standards of modern diagnostics and clinical practice of uterine pathologies
- 182** | **Mariam Tevdorashvili**
David Tevdorashvili
George Tevdorashvili
Nato Metskhvarishvili
Comparative effectiveness of short-course oral metronidazole for bacterial vaginosis in reproductive-age women with vitamin D deficiency: With and without vitamin D therapy
- 183** | **Mariam Tevdorashvili**
David Tevdorashvili
George Tevdorashvili
Nato Metskhvarishvili
Mariam Nemsitsveridze
Tata Skhirtladze
Levonorgestrel-releasing intrauterine device (LNG-IUD) in women with uterine fibroids: A safe and effective option for bleeding control and contraception

CONTENTS

- 185** | **Giorgi Tskrialashvili**
Assessing contralateral tubal patency with hysterosalpingography (HSG) in unilateral tubectomy: A case of pregnancy achieved through contralateral ovulation
- 186** | **Natia Misireli**
Lana Ezieshvili
Natia Pkhaladze
O-rads ultrasound assessment of ovarian and adnexal masses: diagnostic performance and risk stratification
- 188** | **Tamar Kbilashvili**
Mariam Gabadze
Tamar Barbakadze
Tea Charkviani
Thea Pataraia
Mariam Shervashidze
Nino Kutchukhidze
Temiko Zhorzholadze
Ekaterina Volkomorova
Lia Chkonia
Progesterone-primed stimulation vs GnRH antagonists: A comparative review
- 190** | **Alla Vash Margita**
Müllerian anomalies: Current practice and genetic landscape
- 191** | **Tatia Vashakmadze**
Marina Kvelidze
Giorgi Tskrialashvili
Hormonal treatment in catamenial epilepsy: A case report
- 192** | **Lilit Misakyan**
Bacterial biofilms in chronic inflammation:
A hidden factor in reproductive failure and the expanding role of enzyme, hormonal, and microbiome-based therapies
- 194** | **Lali Pkhaladze**
Vittorio Unfer
PCOS phenotypes: A new lens on an old syndrome
- 196** | **Nunu Razmadze**
Adipose tissue and reproductive health: Mechanistic insights and clinical implications in overweight and obese patients

CONTENTS

- 198** | **Samira Taghiyeva**
Modern approaches to the treatment of unexplained infertility:
Individualized protocols, novel markers, and biotechnologies
- 200** | **Nata Nakaidze**
Irma Tedoradze
Dea Nizharadze
Unveiling the role of bacteriophages in gynecology:
a systematic review and case-based analysis
- 201** | **Nutsa Chigladze**
Regnancy following Craniopharyngioma resection
and pituitary atrophy: a rare medical case
- 202** | **Howard Carp, J. A.**
Anticoagulants in recurrent pregnancy loss
- 204** | **Howard Carp, J. A.**
hCG: The forgotten hormone in recurrent pregnancy loss
- 206** | **Tevfik Yoldemir**
Genetic/familial high-risk assessment: Breast & ovarian cancer
- 208** | **Ekaterine Chikhashvili**
Jenaro Kristesashvili
Maia Urjumelashvili
Effectiveness of combined surgical and hormonal therapy
in treatment of endometriomas
- 209** | **Nino Chikobava**
IVF and breast cancer: Myths and reality
- 210** | **Stela Dzotsenidze**
Fertility after unilateral oophorectomy
- 211** | **Natalia Khonelidze**
Gia Tsagareishvili
Maia Koiava
Current state of IVF in Georgia: Trends and challenges
- 212** | **Zurab Marshania**
Nino Nodia
Complex/combined treatment of women with vaginismus:
Evidence-based study

CONTENTS

- 213** | Elisabeth Pkhaladze
Lali Pkhaladze
Nino Davidova
Nani Kvashilava
Archil Khomasuridze
Weight as a modulator of hormonal and metabolic patterns
in classic PCOS across age groups
- 214** | Mariam Shervashidze
Thea Pataraia
Tamar Barbakadze
Tamar Kbilashvili
Mariam Gabadze
Temiko Zhorzholadze
Nino Kutchukhidze
Lia Chkonia
Pregnancy rate in the case of mosaic embryo transfer
- 215** | George Tevdorashvili
Mariami Andguladze
Hormonal correction of menstrual cycle disorders (MCD):
Focus on sex steroids
- 217** | Lali Kharabadze
Marina Koiava
Ultrafast Warming Protocol
- 218** | Mariam Petriashvili
Lasha Tchelidze
Lia Zhorzholiani
Nino Adamia
Evaluating the Link Between Maternal Vitamin D and
Atopic Dermatitis Risk in Offspring
- 220** | Lasha Tchelidze
Nino Kharadze
Nino Khvitia
Ekaterine Mchedlishvili
Manana Pruidze
Natalia Tchiladze
Nino Adamia
Nikoloz Saghirashvili
Infection-Induced Capacitation Disruption: The Role of Trichomonas
Vaginalis in Preeclampsia and Fetal Growth Restriction

CONTENTS

FULL ARTICLES

Supplement to the Abstract Book of the 20th World Congress on Human Reproduction Symposium and Workshop: “Infertility 35+”

224

Tea Charkviani
Jenaro Kristesashvili
Tengiz Zhorzholadze
Nino Kutchukhidze
Tamar Barbakadze
Mariam Gabadze
Tamar Kbilashvili
Mariam Makharadze

Pregnancy outcome after transferring genetically tested embryos vs. non-tested embryos

233

Nato Shamugia
Polina Varlakova
Natalia Podzolkova

Correction of uterine microflora composition disorders and embryo transfer timing in patients with recurrent implantation failure: Clinical effects and prognostic factors

244

Halyna Strelko

Best strategies for egg donor preparation: A retrospective analysis of a single-center cohort

249

Nino Museridze

Combined use of PRP and exosomes in poor responders aged 35-43: A retrospective controlled group study

253

Hasmik Bareghamyan
Tatevik Avagyan
Armine Harutyunyan

Fertility Preservation in an 18-Year-Old Female With an Ovarian Granulosa Cell Tumor: A Case Report

259

Nino Museridze
Madona Jugheli
Ana Chokhonelidze
Bela Jugheli
Nani Tatishvili

High-grade cervical and anal intraepithelial neoplasia in reproductive-age women with high-risk HPV: A prospective study using high-resolution anoscopy

CONTENTS

270	Nino Museridze Madona Jugheli Ana Chokhonelidze Bela Jugheli Nani Tatishvili Prevention of HPV recurrence with HPV vaccination after laser vaporization and conization in reproductive-age patients with HSIL-CIN 2
276	Bidzina Kulumbegov Allergies during pregnancy: Risks, management, and prevention
292	Ramaz Kurashvili Elena Shelestova Gestational diabetes mellitus – from risk factors to prevention
301	Maka Mantskava Nana Momtselidze Giorgi Kuchava Change of rheological status and fibrinogen, as markers of the blood circulatory system, in different pregnancy trimesters
308	Ahmad Karimov Mavlyuda Aliyeva Comparative analysis of vaginal and rectal progestogen administration in pregnant women with threatened miscarriage before 21 weeks of gestation
316	Levan Kobaladze Sofia Andguladze Female orgasmic dysfunction and gynecological pathologies
325	Nia Metonidze Effect of menopause on vitamin D deficiency and COVID-related health outcomes in the female population of Georgia
332	Marina Gvakharia From Near Miss to Never Again: Two Decades of Risk Management and Error Prevention in an IVF Laboratory



It is a great honor for us that in 2025, Georgia will host the **20th World Congress on Human Reproduction**, to be held in Tbilisi from **18 to 21 September 2025** at the *Sheraton Grand Tbilisi Metechi Palace*.

For the first time in history, this prestigious global congress will take place in Eastern Europe.

The Congress is organized by:

- The International Academy of Human Reproduction – under the leadership of Professor Andrea Genazzani
- The Georgian Association of Reproductive Health – under the leadership of Professor Archil Khomasuridze

The Congress is supported by the Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs of Georgia, as well as the Georgian Oncofertility Association.

I am particularly delighted that the annual scientific and medical conference-workshop **“Infertility 35+”**, organized by the Georgian Oncofertility Association and the Georgian-German Reproductive Medicine Center (GGRC), will be held as a symposium within the World Congress on **20-21 September 2025**.

This year, leading physicians and experts from the USA, Canada, Italy, Germany, Spain, Israel, Egypt, Austria, Kazakhstan, Turkey, Ukraine, Armenia, and, of course, Georgia, will present their work.

The main fields covered include reproductive medicine, obstetrics and gynecology, urology, clinical oncology, endocrinology, embryology, and oncosurgery – with hundreds of physicians learning about the latest developments in each area.

Importantly, pre-registered physicians will receive 12 Continuing Professional Development (CME) credit points in addition to the official World Congress certificate.

The scientific papers and abstracts of the speakers will be published in the **Medical Times** – a peer-reviewed medical journal dedicated to reproductive medicine, which publishes the latest research and unites researchers, scientists, and practicing professionals.

The *Medical Times* journal operates on the OJS platform and is assigned a Digital Object Identifier (DOI), ensuring that the published research is disseminated through prestigious international platforms.

We are pleased to have made it possible for Georgian doctors and researchers to publish their articles in the journal completely free of charge. In addition, each participant of the Congress will receive a complimentary copy of the 4th issue of *Medical Times*. The event will also include the presentation of a new book co-authored by me and Professor Vyacheslav Lokshin.

Finally, on behalf of the Georgian Oncofertility Association and the Georgian-German Reproductive Center (GGRC), I sincerely thank you for your presence and your contribution to the development of these medical fields.

Respectfully,

Professor NINO MUSERIDZE

President, Georgian Oncofertility Association

„Georgian-German Reproduction Center” / “ქართული-გერმანული რეპროდუქციული ცენტრი”

 51 g. V. Barnovi st., 0179 Tbilisi / ვ. ბარნოვის ქ. 51 გ, 0179 თბილისი

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ჩვენთვის დიდი პატივია, რომ 2025 წელს საქართველო მასპინძლობს ადამიანის რეპროდუქციის მე-20 მსოფლიო კონგრესს, რომელიც ჩატარდება თბილისში, 2025 წლის 18-21 სექტემბერს, სასტუმრო **Sheraton Grand Tbilisi Metechi Palace**-ში.

პირველად ისტორიაში, ეს პრესტიჟული გლობალური კონგრესი გაიმართება აღმოსავლეთ ევროპაში.

კონგრესის ორგანიზატორები არიან:

- ადამიანის რეპროდუქციის საერთაშორისო აკადემია – პროფესორ ანდრეა ჯენაზანის ხელმძღვანელობით
- საქართველოს რეპროდუქციული ჯანმრთელობის ასოციაცია – პროფესორ არჩილ ხომასურიძის ხელმძღვანელობით

კონგრესს მხარს უჭერს საქართველოს ოკუპირებული ტერიტორიებიდან დევნილთა, შრომის, ჯანმრთელობისა და სოციალური დაცვის სამინისტრო, ასევე საქართველოს ონკოფერტილობის ასოციაცია.

ჩემთვის განსაკუთრებით სასიხარულოა, რომ საქართველოს ონკოფერტილობის ასოციაციისა და ქართულ-გერმანული რეპროდუქციული მედიცინის ცენტრის (GGRC) ორგანიზებით, ყოველწლიური სამეცნიერო-სამედიცინო კონფერენცია-ვორკშოპი „**უნაყოფობა 35+**“ მსოფლიო კონგრესის სიმპოზიუმია და 2025 წლის 20-21 სექტემბერს ჩატარდება.

წელს მოხსენებებით წარსდგებიან მსოფლიოს წამყვანი ექიმები და სფეროს ექსპერტები აშშ-დან, კანადიდან, იტალიიდან, გერმანიიდან, ესპანეთიდან, ისრაელიდან, ეგვიპტიდან, ავსტრიიდან, ყაზახეთიდან, თურქეთიდან, უკრაინიდან, სომხეთიდან და, რა თქმა უნდა, საქართველოდან.

რეპროდუქტოლოგია, მეან-გინეკოლოგია, უროლოგია, კლინიკური ონკოლოგია, ენდოკრინოლოგია, ემბრიოლოგია და ონკოქირურგია – ეს არის ძირითადი მიმართულებები, რომელთა სიახლეების შესახებ ასეულობით ექიმი შეიტყობს.

მნიშვნელოვანია, რომ წინასწარ დარეგისტრირებული ექიმებისთვის, მსოფლიო კონგრესის სერტიფიკატთან ერთად, გაიცემა უწყვეტი პროფესიული განათლების (უპგ) 12 კრედიტ ქულა.

მომხსენებლებთან სამეცნიერო სტატიები და აბსტრაქტები დაიბეჭდება ჟურნალში „**Medical Times**“ – რეპროდუქციული მედიცინის შესახებ სამედიცინო რეცენზირებულ გამოცემაში, რომელიც ეძღვნება უახლესი კვლევების გამოქვეყნებას და აერთიანებს მკვლევარებს, მეცნიერებსა და პრაქტიკოს პროფესიონალებს.

სამეცნიერო ჟურნალი *Medical Times* დაფუძნებულია OJS სისტემაზე და გააჩნია ციფრული ობიექტის იდენტიფიკატორი (DOI), რაც უზრუნველყოფს მასში გამოქვეყნებული კვლევების გავრცელებას პრესტიჟულ საერთაშორისო პლატფორმებზე.

გვინახარია, რომ შევძელით ქართველ ექიმებსა და მკვლევარებს ჟურნალში სტატიების გამოქვეყნება სრულიად უფასოდ შევთავაზოთ. წელს კონგრესის თითოეულ მონაწილეს საჩუქრად გადაეცემა ჟურნალის *Medical Times* მე-4 გამოცემა, ასევე ჩემი და პროფესორი ვიაჩესლავ ლოქშინის ახალი წიგნი.

დასასრულს, საქართველოს ონკოფერტილობის ასოციაციისა და ქართულ-გერმანული რეპროდუქციული ცენტრის (GGRC) სახელით, გულწრფელ მადლობას გიხდით მობრძანებისთვის და თქვენი წვლილისთვის მედიცინის ამ მიმართულებების განვითარებაში.

პატივისცემით,

პროფესორი ნინო მუსარიძე

საქართველოს ონკოფერტილობის ასოციაციის პრეზიდენტი



ABSTRACT BOOK

20th World Congress on Human Reproduction Symposium and Workshop: “Infertility 35+”

18-21 September 2025

Tbilisi, Georgia

VITAMIN D IN FERTILE WOMEN WITH ENDOMETRIOSIS

NINO ABESADZE, PhD Student; **JENARO KRISTESASHVILI**, MD, PhD, Prof.
Department of Obstetrics, Gynecology, and Reproductology, Faculty of Medicine,
Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: Active vitamin D, calcitriol, may play a role in the pathogenesis of endometriosis because of its anti-inflammatory, anti-proliferative effects, and synergy with progesterone. Evidence suggests higher extrarenal 25-hydroxyvitamin-D to calcitriol conversion in women with endometriosis. How this process influences vitamin D metabolite and calcium blood levels remains unclear.

Objective: To evaluate the role of vitamin D in the pathogenesis of endometriosis by analyzing the levels of 25-hydroxy vitamin D, calcitriol, and calcium in patients with endometriosis before and after surgical treatment.

Materials and Methods: 360 fertile women of reproductive age (18-50) were divided into two groups: Group I (n138) patients with surgically and morphologically proven diagnoses of endometriosis and Group II (n222) healthy women of reproductive age. The association between endometriosis, its characteristics, and the blood concentration of 25-hydroxy vitamin D was studied. In 30 women from Group I, a comparative analysis of 25-hydroxyvitamin D, calcitriol, total and ionized calcium was made before and after surgery. Data analyses were made using IBM SPSS 27.

Results: 25-hydroxyvitamin-D levels were significantly lower in women with endometriosis than in healthy women ($p<0.001$). In severe endometriosis, 25-hydroxy-D was lower than in milder forms ($p<0.001$). Dysmenorrhea was negatively associated with 25-hydroxy-D levels ($p=0.01$ $r=-0.449$). In women with endometriosis, calcitriol and total calcium were significantly higher than in healthy women ($p<0.001$) ($p=0.03$). After surgical treatment of endometriosis, calcitriol and total calcium levels were decreased compared to the initial level ($p<0.001$) ($p=0.002$), and 25-hydroxyvitamin D was increased ($p<0.001$).

Conclusion: Women with endometriosis exhibit altered vitamin D and calcium blood levels compared with healthy women. Low 25-hydroxyvitamin D, in conjunction with high calcitriol and calcium, found in endometriosis, does not represent a typical pattern of classic vitamin D de-

ficiency. The tendency of vitamin D and calcium normalization after surgery indicates that the presence of endometriosis influences vitamin D and calcium blood levels. Our results suggest that endometriosis could lead to 25-hydroxyvitamin D deficiency itself, due to extrarenal calcitriol production, which enters the bloodstream and causes hypercalcemia.

Keywords: endometriosis; calcitriol; 25-hydroxy-D vitamin 25OHD; $1.25(\text{OH})^2\text{D}$

SILENT INHABITANTS: EXPLORING THE ROLE OF THE ENDOMETRIAL MICROBIOME IN IMPLANTATION FAILURE AND ART SUCCESS

ANA AIVAZOVA, MD

Gynecologist, Reproductive Specialist, Tbilisi, Georgia

ABSTRACT

Background: The endometrial microbiome has emerged as a critical yet understudied factor in endometrial receptivity and implantation success. Traditionally considered sterile, the endometrial cavity is now known to harbor a distinct microbial community, which may influence outcomes in assisted reproductive technologies (ART), particularly in cases of recurrent implantation failure (RIF).

Methods: This review synthesizes current literature from peer-reviewed clinical and translational studies examining the composition, diversity, and function of the endometrial microbiota in fertile versus infertile women. Special focus is placed on studies using next-generation sequencing (NGS) to characterize microbial profiles and assess correlations with ART outcomes. Mechanistic data from immunological and transcriptomic studies were also evaluated to understand host-microbiome interactions.

Results: Multiple studies have shown that a Lactobacillus-dominant endometrial microbiome is associated with higher implantation and pregnancy rates, while dysbiosis – characterized by the presence of Gardnerella, Atopobium, and other anaerobes – correlates with RIF and decreased ART success. Emerging data suggest that the endometrial microbiota may modulate local immune responses, endometrial receptivity, and cytokine signaling. Preliminary interventional studies using antibiotics or probiotics show potential to restore microbial balance, though larger randomized trials are needed.

Conclusion: The endometrial microbiome represents a promising biomarker and therapeutic target for enhancing ART outcomes. Integrating microbial profiling into fertility care may offer a novel, personalized approach to managing implantation failure. Further research is needed to standardize diagnostic criteria, clarify causal relationships, and develop effective microbiome-modulating interventions.

Keywords: endometrial microbiome; recurrent implantation failure; assisted reproductive technology; lactobacillus; dysbiosis; reproductive outcomes

ფარული გაცხობრება: ენდომეტრიუმის მიკრობიომის როლი იმპლანტაციის წარუმატებლობასა და დამხმარე რეპროდუქციული ტექნოლოგიების (ART) წარმატებაში

ანა აივაშოვა

გინეკოლოგი, რეპროდუქტოლოგი, თბილისი, საქართველო

აბსტრაქტი

შესავალი: ენდომეტრიუმის მიკრობიომი სულ უფრო მეტად განიხილება როგორც მნიშვნელოვანი ფაქტორი რეპროდუქციულ წარმატებაში. ხანგრძლივი დროის განმავლობაში ენდომეტრიუმი სტერილურ გარემოდ მიიჩნეოდა, თუმცა უახლესი კვლევების მიხედვით, იგი მასპინძლობს უნიკალურ მიკრობულ გარემოს, რომელიც შესაძლოა მნიშვნელოვან გავლენას ახდენდეს როგორც იმპლანტაციის პროცესზე, ისე ART-ის შედეგებზე, განსაკუთრებით განმეორებითი იმპლანტაციის წარუმატებლობის (RIF) შემთხვევაში.

მეთოდები: წარმოდგენილია უახლესი სამეცნიერო ლიტერატურის მიმოხილვა, მათ შორის კლინიკური და მოლეკულური კვლევები, რომლებიც ეფუძნება ახალი თაობის სეკვენირებას (NGS). ყურადღება მახვილდება ენდომეტრიუმის მიკრობული პროფილის შედარებაზე ფერტილურ და უნაყოფო პაციენტებში, ასევე იმუნური და ციტოკინური მექანიზმების ურთიერთქმედების ანალიზზე.

შედეგები: კვლევების მიხედვით, ენდომეტრიუმში *Lactobacillus*-ის დომინანტობა ასოცირდება იმპლანტაციისა და ორსულობის მაღალ მაჩვენებლებთან. ამასთან, დისბიოზი, რომელიც ხასიათდება ისეთი მიკროორგანიზმებით, როგორიცაა *Gardnerella Atopobium*, ხშირად აღინიშნება იმპლანტაციის წარუმატებლობისა და ART-ის დაბალი ეფექტიანობის შემთხვევაში. წინასწარი ინტერვენციული მიდგომები ანტიბიოტიკებისა და პრობიოტიკების გამოყენებით იძლევა პერსპექტიულ შედეგებს, თუმცა საჭიროებს დამატებით კვლევებს.

დასკვნა: ენდომეტრიუმის მიკრობიომი წარმოადგენს მნიშვნელოვან ბიომარკერს და თერაპიულ სამიზნეს რეპროდუქციული მედიცინის თანამედროვე პრაქტიკაში. მიკრობიომის შეფასების ინტეგრირება ART-ის დაგეგმვასა და მართვაში შეიძლება გახდეს პერსონალიზებული მიდგომის ნაწილი იმპლანტაციის წარუმატებლობის მკურნალობაში. საჭიროა დამატებითი კვლევები მიკრობიომის დიაგნოსტიკური სტანდარტების ჩამოსაყალიბებლად და სამკურნალო სტრატეგიების გასაუმჯობესებლად.

საკვანძო სიტყვები: ენდომეტრიუმის მიკრობიომი; განმეორებითი იმპლანტაციის წარუმატებლობა; დამხმარე რეპროდუქციული ტექნოლოგია; *Lactobacillus*; დისბიოზი; რეპროდუქციული შედეგები

ENHANCING PGT-A SUCCESS AND MINIMIZING BIAS: THE PROMISE OF A PREMIUM APPROACH

SULEYMAN AKTUNA, PhD

Mikrogen Genetic Diagnosis Laboratory, Ankara, Türkiye

ABSTRACT

Preimplantation genetic testing for aneuploidy (PGT-A) improves ART outcomes by identifying chromosomally normal embryos before transfer. However, conventional methods face limitations, including interpretive variability, inconclusive results, maternal contamination, and the inability to detect abnormalities such as triploidy reliably. These factors can lead to embryo misclassification, unnecessary discards, or cancelled cycles.

A premium PGT-A approach integrates advanced sequencing technologies, refined bioinformatics, and SNP-based quality control to enhance reliability without requiring parental DNA. By incorporating hundreds of informative SNPs across the genome, this strategy improves chromosomal assessment, reduces technical artifacts, and increases confidence in embryo selection. A key advantage is accurate detection of triploidy (69, XXX), which may otherwise be misclassified as normal female (46, XX). Through tri-allelic microhaplotype and allele frequency analysis, triploid embryos are correctly identified, preventing transfer of nonviable embryos.

Maternal contamination detection is another critical feature. Contamination from cumulus cells during biopsy can compromise results; SNP-based methods identify such cases early, allowing rebiopsy and preserving viable embryos that would otherwise be discarded. The use of SNPs also reduces "no result" outcomes caused by amplification failures, providing a more precise distinction between technical noise and accurate biological signals.

Additional benefits include sibling embryo tracking through SNP clustering, which strengthens identity verification, reduces mix-up risk, and avoids separate paternity testing. Clinically, SNP-enriched PGT-A delivers greater diagnostic precision, improved detection of complex abnormalities, and more equitable embryo utilization.

Premium PGT-A represents a significant advancement toward personalized ART – supporting higher implantation rates, fewer miscarriages, and healthier live births through more accurate, reproducible, and patient-centered embryo selection.

Keywords: triploidy detection; maternal contamination; premium PGT-A; sibling QC; polyploidy; single nucleotide polymorphisms

ENHANCING GENETIC DIAGNOSIS AND ANEUPLOIDY SCREENING IN PGT-M CYCLES FOR IMPROVED CLINICAL OUTCOMES

EVİRİM ÜNSAL, MD, PhD

*Mikrogen Genetic Diagnosis Laboratory; Department of Clinical Genetics,
Faculty of Medicine, Yüksek İhtisas University, Türkiye*

ABSTRACT

Preimplantation Genetic Testing (PGT) has evolved from single-gene PCR analysis to advanced methods combining monogenic disease testing (PGT-M) with aneuploidy screening (PGT-A). Technological progress, particularly Whole Genome Amplification (WGA), trophectoderm biopsy, and vitrification, now allows simultaneous evaluation of mutations and chromosomal status, thereby improving embryo selection and clinical outcomes.

Two main strategies are applied in PGT-M cycles. Traditional multiplex nested PCR is reliable but limited, especially when aneuploidy testing is needed. WGA-based approaches enable both PGT-M and PGT-A, either sequentially or concurrently, but may suffer from Allele Drop-Out (ADO) and uneven coverage. Using trophectoderm biopsies of 5-7 cells reduces ADO from about 25% in blastomere biopsies to 5%, increasing diagnostic reliability.

Clinical studies highlight the value of integrating PGT-A into PGT-M cycles. Even in young carriers of single-gene disorders, miscarriage risk remains elevated. Adding PGT-A improves pregnancy rates (45% to 68%) and lowers miscarriages (15% to 5%). Moreover, concurrent testing reveals that up to 50% of embryos are aneuploid, with nearly 75% unsuitable for transfer due to combined genetic findings. These data emphasize that morphology alone is insufficient for embryo selection.

Therefore, concurrent PGT-M and PGT-A should be considered standard practice whenever a biopsy is performed. This combined strategy enhances implantation and live birth rates, prevents inadvertent transfer of aneuploid embryos, and provides families with more reliable reproductive counseling. Continued improvements in WGA will further expand the accuracy and applicability of these integrated genetic screening approaches.

Keywords: PGT-M; PGT-A; whole Genome Amplification; aneuploidy screening; trophectoderm biopsy

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FROM IVF TO GENETICS: ENHANCING IVF LABORATORY MONITORING AND SAFETY

VOLKAN BALTACI, MD, PhD

Mikrogen Genetic Diagnosis Laboratory, Çankaya, Ankara, Turkey

ABSTRACT

IVF laboratories still depend heavily on operator-driven processes. Manual handling, subjective assessments, and limited real-time controls introduce risks of inconsistency and compromise patient safety. Despite the availability of advanced instruments, key performance indicators (KPIs) and quality benchmarks remain underused in routine embryology.

This presentation introduces a framework for integrating digital monitoring systems, traceable automation, and evidence-based KPIs into IVF workflows, from oocyte retrieval to embryo transfer and biopsy. Several new technologies are explored, including wireless barcoded witnessing to prevent mismatches, smart biopsy devices with real-time alerts and laser distance controls, incubator-compatible time-lapse systems for standardized embryo assessment, and high-capacity cryo-storage solutions that improve logistics and traceability.

These tools, anonymized to avoid brand attribution, align with ESHRE's 2024 guidelines on laboratory safety and traceability. Each tool is evaluated for its impact on laboratory metrics, including error reduction, fertilization consistency, workflow efficiency, and traceability of documentation. Benchmarking strategies are proposed to monitor reproducibility across multiple IVF centers.

By applying principles from molecular diagnostics, sample traceability, barcode-based identity verification, and digital audit trails, IVF laboratories can enhance precision, transparency, and accountability. Embedding these standards into daily embryology tasks reduces manual errors, improves reproducibility, and secures a traceable chain of custody for every biological sample.

This genetics-driven safety approach aims to establish a new paradigm in IVF laboratory practice, ensuring that technological progress translates into measurable improvements in both laboratory performance and patient outcomes.

Keywords: IVF laboratory safety; KPIs; automation in IVF; electronic witnessing; mismatch

ROLE OF ENDOMETRIAL RECEPTIVITY ANALYSIS IN ENHANCING ART OUTCOMES FOR ADVANCED-AGE PATIENTS

TAMAR BARBAKADZE, MD;¹ JENARO KRISTESASHVILI, MD, PHD;^{2,3}

**MARIAM SHERVASHIDZE;¹ THEA PATARAIA; TAMAR KBILASHVILI;¹ MARIAM GABADZE;
TEMIKO ZHORZHOLADZE, MD;¹ NINO KUTCHUKHIDZE; NINA KIM; LIA CHKONIA, MD¹**

¹ Georgian-American Center for Reproductive Medicine (ReproART), Tbilisi, Georgia

² Faculty of Clinical and Translational Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

³ Clinic "Universe", Tbilisi, Georgia

ABSTRACT

Background: With more women delaying childbearing, fertility outcomes in advanced-age patients remain suboptimal, even with donor oocytes, mainly due to endometrial ageing. Recurrent implantation failure (RIF) is a significant challenge in ART, especially among older patients. High-quality euploid embryos and optimal endometrial-embryo synchrony are essential for success.

Objective: To evaluate whether personalized embryo transfer (pET), guided by Endometrial Receptivity Analysis (ERA), improves ART outcomes in advanced-age RIF patients using donor oocytes and Preimplantation Genetic Testing for Aneuploidy (PGT-A).

Materials and Methods: A randomized, controlled observational follow-up study was conducted from 2020 to 2023. After obtaining informed consent, 320 patients with RIF were selected. Patients were allocated into the study group and control group 1 based on consistent application of randomization principles, while control group 2 was chosen separately. The study group included patients undergoing PGT-A and ERA, aged 35-45 years, with a mean age of 40.5 ± 3.7 years. Control group 1 comprised patients undergoing PGT-A, aged 35-45 years, with a mean age of 40 ± 4.2 years. Control group 2 consisted of patients undergoing PGT-A and ERA, aged less than 35 years, with a mean age of 31.6 ± 2.2 years.

Results: Results suggest that ERA may improve implantation and pregnancy outcomes in advanced-age patients, particularly those with RIFs. The pregnancy rate was significantly higher in the study group (77.9%) compared to control group 1 (57.6%) ($p=0.0007$), and no significant difference compared to control group 2 (77.3%) ($p=0.94$). The implantation rate was higher in the study group (54.1%) than in control group 1 (39.4%) ($p=0.0009$), and there was no signifi-

cant difference between the study group and control group 2 (50%, $p=0.87$). The live birth rate was also higher in the study group (71.3%), compared to control group 1 (39.4%) ($p<0.0001$). There were no significant differences between the study group and control group 2 (65.9%, $p=0.50$).

Conclusions: pET guided by ERA significantly improves pregnancy, implantation, and live birth rates in advanced-age patients with challenging reproductive histories. pET provides ART outcomes with no significant difference between advanced-age patients and younger patients with pET guided by ERA.

Keywords: Recurrent Implantation Failure (RIF); ERA; ageing of the endometrium; oocyte donation; PGT-A

GNRH ANTAGONISTS VS. PROGESTIN-PRIMED OVARIAN STIMULATION (PPOS): IS IT TIME TO CHANGE PROTOCOLS?

IDO BEN-AMI, MD, PhD, Prof.

*Department of Obstetrics, Gynecology, and Infertility; Managing Director,
Shaare Zedek Medical Center, Jerusalem, Israel*

ABSTRACT

Background: Progestin-primed ovarian stimulation (PPOS) has emerged as a convenient and potentially less burdensome alternative to GnRH antagonist protocols in IVF. However, concerns remain regarding its impact on embryo quality and cumulative live birth rates (CLBR).

Methods: This presentation reviews data from multiple retrospective cohort studies and non-inferiority trials comparing PPOS – primarily using medroxyprogesterone acetate (MPA) – to GnRH antagonist protocols. Populations included unselected patients, oocyte donors, women with PCOS, diminished ovarian reserve, and those undergoing preimplantation genetic testing (PGT).

Results: PPOS effectively suppressed premature LH surges and was associated with similar oocyte yields and gonadotropin usage. However, several studies demonstrated lower cumulative live birth rates (CLBRs) and reduced good-quality blastocyst rates in the PPOS group. Additionally, the time to live birth was longer with PPOS compared to GnRH antagonist protocols. In one propensity score-matched study (n=2,848), the GnRH antagonist group had significantly lower cycle cancellation rates and higher CLBRs ($P<0.001$). In predicted suboptimal responders, a non-inferiority trial did not confirm PPOS as equivalent in live birth outcomes. Single-cell RNA sequencing indicated potential alterations in mitochondrial gene expression, raising concerns about possible oocyte quality compromise with PPOS.

Conclusion: While PPOS offers logistical advantages and patient comfort, current evidence supports GnRH antagonist protocols as the more effective option for optimizing live birth outcomes in IVF, particularly in unselected and suboptimal responder populations.

Keywords: progestin-primed ovarian stimulation (PPOS); GnRH antagonists; in vitro fertilization (IVF); cumulative live birth rate (CLBR); oocyte quality; luteinizing hormone suppression

FROZEN EUPLOID SINGLE EMBRYO TRANSFER: FACTORS FROM RETRIEVAL AND FET CYCLES THAT INFLUENCE LIVE BIRTH OUTCOMES

DAVID H. MCCULLOH, PhD, HCLD, CC; **CAROLINE MCCAFFREY**, PhD, HCLD;

JAMES A. GRIFO, MD, PhD

NYU Langone Fertility Center, New York, NY, USA

ABSTRACT

Context: Selection of euploid embryos for transfer following preimplantation genetic testing for aneuploidy (PGT-A) improves live birth rates. The day, stage, and grades of blastocysts are often used to improve selection; however, other features of retrieval and embryo transfer cycles have been less studied.

Objective: We examined the association of 40 parameters involved with patient monitoring and embryology with live births following single-thawed euploid embryo transfers (STEETs).

Materials and Methods: Multiple logistic regression was used to fit three models: Model 1 used only blastocyst day, stages, and grades; Model 2 used parameters chosen using Akaike information criteria; Model 3 used all 40 available parameters. Standard partial regression coefficients assessed the relative contributions of parameters to the models. Training data (70% [1469] cycles) were randomly chosen from 2099 STEETs between 2015 and 2020. Receiver operator characteristic (ROC) curves compared predictive values of models using training or test data (547 remaining cycles).

Results: Blastocyst day, stage, ICM, and TE grades were significant predictors in Model 1 and were 4 of the 6 most essential contributors to Model 2. Patient age and letrozole use from the retrieval cycle, as well as performance of AZH, the estradiol level on the day prior to progesterone start (in the FET cycle), the number of embryos biopsied on days 5 and 6, and the progesterone level on the day of FET were also significant contributors to Model 2. ROC curves revealed Model 2 was the best with the training data, but revealed minimal improvements for Models 2 and 3 using test data. Next, we examined the association of these 40 parameters with three sequential steps of success: Implantation (elevated hCG), clinical pregnancy (hCG progressing to visualization of a fetal sac – the converse of biochemical loss), and live birth (fetal sac progressing to live birth – the converse of clinical pregnancy loss). The parameters identified were differentially associated with these sequential steps (using fitting methods analogous to Model 2).

Conclusion: Judicious selection of parameters predicts outcome better than using all available parameters. Parameters from embryo descriptions, the retrieval cycle, the uterine preparation cycle, and the thaw were associated with the outcomes, indicating that embryo description alone is insufficient to predict outcome. The ability to predict outcomes for STEETs was relatively poor, suggesting that other, unidentified parameters may influence the outcome of STEETs.

Keywords: IVF; ovarian stimulation; FET success; uterine preparation; PGT-A; ROC curve

POSSIBILITIES FOR IMPROVING IVF OUTCOMES IN WOMEN WITH UNEXPLAINED INFERTILITY AND DIMINISHED OVARIAN RESERVE

TATIANA NAZARENKO

ABSTRACT

Study Question: This study aimed to evaluate whether intraovarian injection of MSC-derived extracellular vesicles (EVs) improves the outcomes of IVF in women with unexplained infertility who exhibit manifestations of diminished ovarian reserve (DOR).

EV therapy increased the number of mature oocytes and embryos reaching the cleavage stage.

What Is Known Already: Unexplained infertility is often associated with a poor ovarian response to controlled ovarian stimulation (COS). Consequently, this condition leads to high cancellation rates and a significant decline in pregnancy rates during IVF cycles. Moreover, the literature lacks targeted studies exploring the association between unexplained infertility and decreased ovarian reserve in young infertile women. Given the complex ovarian dynamics and challenges such as unexplained infertility and DOR, stem cell therapy – particularly the use of EVs – shows promise. EVs act via paracrine mechanisms through microRNAs and bioactive molecules, suppressing apoptosis, stimulating angiogenesis, and activating latent regenerative potential. Key microRNAs influence estrogen secretion, cellular proliferation, and apoptosis resistance. EVs, therefore, present novel possibilities for treating complex cases of infertility.

Study Design, Size, Duration: In the retrospective stage of the study, clinical and anamnestic data from 1,500 married couples were analyzed. These couples underwent 2,156 stimulated cycles between 2020 and 2022 at the V.I. Kulakov National Medical Research Center for Obstetrics, Gynecology, and Perinatology. Two main groups were identified: Group 1 included patients with an established cause of infertility, while Group 2 included patients with unexplained infertility (UI)

The first step was to evaluate whether young women <40 years of age with unexplained infertility exhibit manifestations of DOR compared to adequately matched controls in an assisted reproduction setting.

The primary study group involved 120 infertile women aged 20 to 40 years, each with unexplained infertility and manifestations of diminished ovarian reserve, and a history of at least two unsuccessful IVF cycles. These participants were enrolled during their subsequent IVF

cycle. Before inclusion, all patients provided written informed consent in accordance with a protocol approved by the institutional ethics committee.

Participants/Materials, Setting, Methods: Of the 156 married couples referred for IVF treatment, UI was diagnosed. Additionally, 120 patients <38 years of age with primary UI were selected from the observation group. These patients had a history of repeated IVF failure due to poor ovarian response to COS or the absence of embryos suitable for transfer.

Patients in Group 1 (n=60) received treatment with exosomes derived from human umbilical cord mesenchymal stem cells (HUC-MSCs-Exos) before initiating their IVF cycle. Patients in Group 2 did not receive specific treatment. Comparative analysis encompassed antral follicle count (AFC), anti-Müllerian hormone (AMH) levels, follicle-stimulating hormone (FSH) levels, ovarian stimulation outcomes, and the primary characteristics of oogenesis, embryogenesis, and pregnancy rates.

Main Results and the Role of Chance: Women ≤38 years of age with unexplained infertility exhibited suboptimal ovarian reserve compared with controls, as evidenced by lower basal AMH levels, AFC, ovarian response to COS, and IVF outcomes. Women with unexplained infertility had higher baseline FSH, lower AMH, and lower AFC than controls (**P=0.001**). The oocyte yield was also lower in the unexplained infertility group (P=0.001).

Patients with the poorest IVF outcomes were characterized by both a small number of obtained oocytes and repeated embryogenesis arrest.

In the leading study group, after exosomal treatment, improvement in reproductive outcomes was more significant. FSH concentration was significantly different before and 30 days after the procedure in both groups. In Group 1, FSH values decreased in 79% of cases. AMH levels did not change significantly in either group. The AFC increased in Group 1 compared with Group 2. All patients underwent an IVF antagonist cycle one month after treatment. The number of oocytes obtained in Group 1 ranged from 2 to 12, with MII oocytes ranging from 1 to 11; in Group 2, the range was 0-8, with MII oocytes ranging from 0 to 7. The number of blastocysts in Group 1 ranged from 1 to 5, while in Group 2, it ranged from 0 to 2.

Limitations, Reasons for Caution: Further research with fundamental approaches is required to understand the results better.

Broader Implications of the Findings: EVs improved both ovarian reserve measures and IVF outcomes. Their clinical application may enhance reproductive outcomes in patients for whom donor oocytes were previously the only option.

Keywords: assisted reproductive technology; diminished ovarian reserve; extracellular vesicles; infertility; In vitro fertilization; mesenchymal stem cells; unexplained infertility



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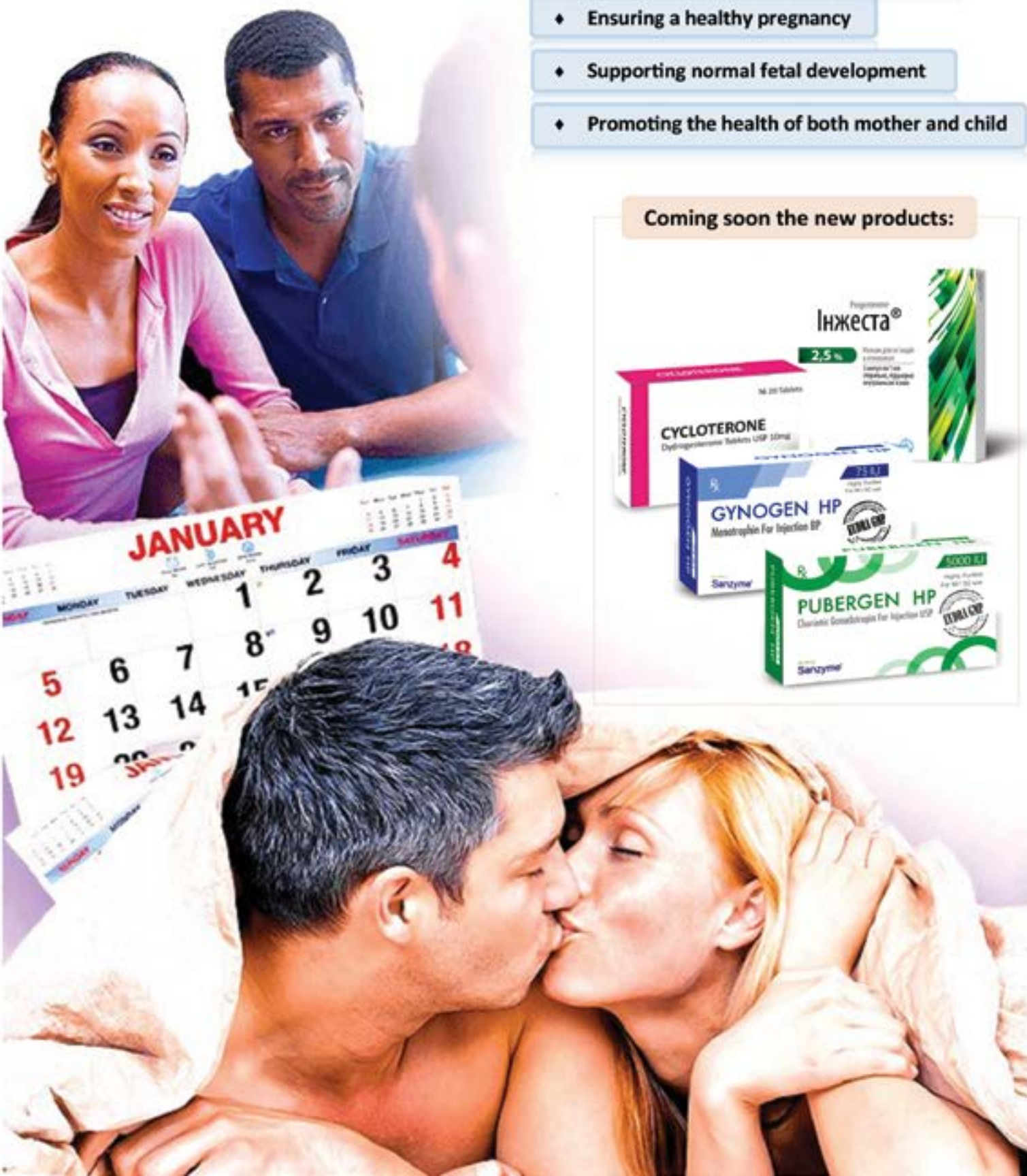


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FRESH VERSUS FROZEN, WHEN AND TO WHOM?

RAOUL ORVIETO, MD, MMSc^{1, 2}

¹ *Department of Obstetrics and Gynecology, Chaim Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel;*

² *Tarnesby-Tarnowski Chair for Family Planning and Fertility Regulation, Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

In recent years, there has been a rise in the practice of elective freezing of all good-quality embryos and transfer in subsequent cycles. This shift is largely attributed to advancements in cryopreservation techniques, the adoption of the GnRH agonist trigger, and the implementation of PGT-A. Numerous studies have investigated the potential benefits of the freeze-all approach in patients undergoing IVF. The findings suggest that this strategy does not lead to improved IVF outcomes for low responders, while evidence remains conflicting for regular and high responders. From a safety perspective, elective frozen embryo transfer (FET) significantly reduces the risk of moderate and severe OHSS; however, it is associated with a higher risk of pre-eclampsia. In this presentation, we aim to assess whether elective FET offers advantages in terms of reproductive, obstetric, and perinatal outcomes when compared to fresh embryo transfer in IVF/ICSI cycles. Furthermore, we will examine the efficacy of elective FET versus fresh embryo transfer across various subgroups of patients undergoing an ART cycle.

Keywords: cryopreservation; freeze-all; fresh transfer; FET; pregnancy complication; live birth

OPTIPREDICT IVF: AN AI-POWERED PLATFORM FOR PERSONALIZED CONTROLLED OVARIAN STIMULATION – EXPERIENCE FROM A UKRAINIAN CLINIC

VIKTORIYA YUZKO, MD, TAMARA A. YUZKO, MD, PhD, OLEKSANDR SAMBOLSKYI
Medical Center for Infertility Treatment, Chernivtsi, Ukraine

ABSTRACT

Background: Physicians in reproductive medicine face daily challenges in designing personalized controlled ovarian stimulation (COS) protocols. This task involves analyzing multiple parameters and may take up to an hour per patient.

Objective: To develop a digital tool that assists physicians in generating COS protocols more efficiently, accurately, and in a patient-friendly format.

Materials and Methods: The Yuzko Medical Center team developed OptiPredict IVF, an artificial intelligence (AI)-based digital assistant. Using clinical guidelines (ESHRE/ASRM) and patient-specific data, the system generates stimulation protocols, explanations, and individualized treatment PDFs. A pilot implementation included retrospective analysis of 100 IVF cycles (Jan-Mar 2025) and prospective analysis of 50 IVF cycles (Apr-May 2025).

Results: Protocol preparation time decreased by 40% (from 60 to 36 minutes). Patient compliance increased from 62% to 87%, and satisfaction rose from 4.2 to 4.8 out of 5. Prediction-to-outcome correlation reached 0.92. Daily consultation capacity increased by 30%.

Conclusions: OptiPredict IVF enhances physician performance by streamlining routine tasks without replacing clinical decision-making. The platform increases efficiency, supports personalized care, and improves patient understanding.

Keywords: IVF, artificial intelligence, digital assistant, ovarian stimulation, compliance, reproductive medicine innovation.

Acknowledgments

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Conflict of Interest

The authors are developers and/or clinical users of the OptiPredict IVF platform. All potential conflicts have been disclosed.

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LONG-TERM OUTCOMES FOR CHILDREN FOLLOWING INTRAPARTUM COMPLICATIONS: ANALYSIS OF LEADING RISK FACTORS IN HIGH-RISK WOMEN, INCLUDING THOSE UNDERGOING IVF

ASYMBEKOVA G. U., MD; ABEKOV K. D., MD; ASYMBEKOVA A. SH., MD; IBRAIMOVA R. N., MD; CHINALIEV I. S., MD

ABSTRACT

Background: Intrapartum complications such as hypoxia, prematurity, and severe perinatal asphyxia remain the leading causes of neurological, somatic, and cognitive disorders in children. Recent research has convincingly demonstrated that complications arising during labor and delivery exert the greatest impact on offspring health, regardless of conception method or pregnancy course. This is relevant for women who have undergone in vitro fertilization (IVF) as well as for spontaneous pregnancies with complicated histories.

Aim: To analyze the long-term outcomes for children associated with intrapartum complications and identify the leading risk factors in a high-risk cohort of women, including those who underwent IVF.

Materials and Methods: The study included data from women classified as high perinatal risk, among them 118 women who underwent IVF procedures. A retrospective analysis was performed of labor characteristics, the structure and frequency of complications (fetal hypoxia, preterm birth, neonatal asphyxia, and adaptation disorders). The impact of these complications on the development of neurological (cerebral palsy, psychomotor and cognitive delay, epilepsy), somatic (respiratory, cardiovascular, endocrine disorders), and psycho-emotional disorders in children was investigated.

Results: It was demonstrated that intrapartum complications (hypoxia, prematurity, asphyxia, and severe perinatal events) were the key determinants of long-term outcomes for children. The most pronounced impairments were observed in neonates who experienced acute forms of hypoxia and asphyxia, regardless of the pregnancy course or conception method. Children born following complicated deliveries had a significantly higher incidence of neurological deficits, developmental delays, cognitive dysfunction, and somatic diseases, whereas IVF procedures or maternal comorbidities alone did not exert a decisive influence on long-term prognosis. Similar patterns were observed among women without IVF in the presence of severe intrapartum complications.

Conclusion: The findings confirmed that long-term outcomes for child health are primarily associated with intrapartum complications, rather than pregnancy complications, maternal co-

morbidities, or the use of IVF. These results emphasize the need to focus obstetric strategies on timely diagnosis and management of intrapartum complications, which is crucial for improving long-term prognosis in high-risk offspring. The findings are of practical importance for developing surveillance and medical support programs for children who have experienced severe birth complications, regardless of conception method.

Keywords: intrapartum complications; in vitro fertilization (IVF); hypoxia; neonatal asphyxia; long-term child outcomes; neurological and cognitive disorders

CRITICAL ANALYSIS OF ANTENATAL CARE IN SINGLETON IVF PREGNANCIES IN GEORGIA: POLYPHARMACY, IATROGENIC COMPLICATIONS, AND QUALITY ASSESSMENT

TAMAR ANTELAVA, MD, PhD

Head of CME Education and Quality Assessment, Evex, Tbilisi, Georgia

ABSTRACT

Objective: This study aimed to conduct a critical analysis of the specific characteristics of antenatal care in Georgia for singleton pregnancies conceived through in vitro fertilization (IVF), with particular attention to identifying patterns of polypharmacy, iatrogenic complications, and irrational management, to propose strategies for improving care quality.

Methods: We reviewed randomly selected medical records of pregnant women, assessing aspects such as risk stratification, timely detection of complications, prevention strategies, management approaches, and the rationale for medication selection.

Results: The analysis revealed inadequate risk assessment practices, with all cases classified as high-risk pregnancies, contrary to current international recommendations. Evidence indicates that IVF pregnancies should not be universally categorized as high-risk, as the frequency of complications in singleton IVF pregnancies is comparable to that in spontaneously conceived pregnancies. Increased complication rates among IVF pregnancies were found to be associated with multiple gestations, advanced maternal age, and pre-existing comorbidities. Preventive strategies for these complications are analogous to those used in spontaneously conceived pregnancies. A high prevalence of polypharmacy (>8%) was identified, along with insufficient communication among healthcare professionals during patient management. The study also identifies interventions for overdiagnosis, excessive pharmacological intervention, and miscommunication between providers.

Conclusion: Optimization of IVF pregnancy management is strongly dependent on a multidisciplinary approach, with enhanced communication between obstetricians and reproductive specialists. Regular retrospective institutional reviews are also recommended. These measures are expected to improve both maternal and perinatal outcomes significantly.

Keywords: in vitro fertilization; antenatal care; singleton pregnancy; polypharmacy; iatrogenic complications; risk assessment; maternal and perinatal outcomes

GENETIC AND METABOLIC IMPACT IN PCOS: MTHFR POLYMORPHISMS, HOMOCYSTEINE, INSULIN RESISTANCE, AND PREGNANCY OUTCOME

ELENE ASANIDZE, MD, PhD, Ass. Prof.;¹ **ZURAB R. TSETSKHLADZE**, PhD, Prof.;²
JENARO KRISTESASHVILI, MD, PhD, Prof.;³ **MANANA URJUMELASHVILI**, MD, PhD;¹
MALKHAZ VAKHANIA, PhD²

¹ University Geomedi, Tbilisi, Georgia

² Scientific-Research Institute of Experimental and Clinical Medicine, University Geomedi, Tbilisi, Georgia

³ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Recurrent pregnancy loss (RPL) in polycystic ovary syndrome (PCOS) is a complex obstetric complication influenced by genetic, metabolic, and endocrine factors. Insulin resistance plays a key role in adverse pregnancy outcomes, including RPL, by contributing to endothelial dysfunction, inflammation, and impaired placental development. Research has explored the impact of hyperhomocysteinemia and **MTHFR gene polymorphisms** on PCOS, particularly their link to insulin resistance, but findings remain inconsistent.

Objective: To determine the association between homocysteine levels, MTHFR C677T and A1298C polymorphisms, insulin resistance, and pregnancy outcomes in women with PCOS.

Materials and Methods: This case-control comparative study included 177 women: 96 with PCOS and 81 age-matched controls without PCOS. Participants were divided into 4 groups:

- **Group I:** 59 PCOS patients with RPL
- **Group II:** 37 PCOS patients with live birth history and no RPL
- **Group III:** 39 women with RPL, without PCOS
- **Group IV (controls):** 42 women with live birth history, without RPL and PCOS

Groups were compared for serum homocysteine (Hcy) levels and the presence of 2 common MTHFR single-nucleotide polymorphisms (SNPs): C677T and A1298C.

Results: PCOS patients had significantly higher mean homocysteine levels, frequency of hyperhomocysteinemia, and prevalence of MTHFR polymorphisms compared with non-PCOS participants ($p < .05$). Group I (PCOS with RPL) showed significantly elevated Hcy ($13.7 \pm 2.7 \mu\text{mol/L}$) compared with Group II (10.3 ± 2.6), Group III (11.5 ± 2.3), and Group IV (7.3 ± 2.2) ($p < .001$). In Group I, the frequencies of the C677T-CT, A1298C-AC genotypes, and compound hetero-

zygosity (C677T-CT/A1298C-AC) were significantly higher than in other groups ($p < .05$). The prevalence of MTHFR A1298C (CC) was significantly higher in Group II compared with other groups ($p < .05$). A significant positive correlation was observed between Hcy and HOMA-IR in PCOS patients with RPL ($p < 0.05$).

Conclusions: Hyperhomocysteinemia, MTHFR polymorphisms (C677T and A1298C), and insulin resistance are significantly associated with adverse pregnancy outcomes in PCOS. These findings suggest that genetic and metabolic factors contribute to increased risk of pregnancy complications, particularly RPL, in women with PCOS.

Keywords: polycystic ovary syndrome; MTHFR polymorphisms; homocysteine; recurrent pregnancy loss; insulin resistance

OVARIAN ENDOMETRIOSIS: THE NEED FOR PERSONALIZED MANAGEMENT

MANANA GEGECHKORI, MD, PhD

Zurab Sabakhtarashvili Reproductive Clinic, Tbilisi, Georgia

ABSTRACT

Ovarian endometriosis presents a persistent challenge in gynecologic practice, particularly among women desiring future fertility. Personalized management based on age, ovarian reserve, symptomatology, and reproductive goals is essential. A judicious approach that minimizes surgical harm while controlling disease progression – particularly through personalized, pathogenesis-based hormonal therapy – offers the best prospects for maintaining reproductive health and preventing recurrence.

Keywords: ovarian endometriosis; personalized management; fertility preservation; hormonal therapy; gynecology; recurrence prevention

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REASONABLE AND RATIONAL THERAPY OF MENSTRUAL DISORDERS

LALI PKHALADZE, MD; NANA CHOPIKASHVILI, MD

Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: The menstrual cycle is a sensitive indicator of a woman's health, with significant implications for physical, emotional, and reproductive well-being. Menstrual disorders – including oligomenorrhea, amenorrhea, heavy menstrual bleeding, and dysmenorrhea – are frequently associated with underlying hormonal imbalances.

The International Federation of Gynecology and Obstetrics (FIGO) has introduced standardized classification systems to facilitate the management of menstrual disturbances. The PALM-COE-IN system categorizes abnormal uterine bleeding (AUB) into structural and nonstructural causes. The updated FIGO HyPO-P classification of ovulatory disorders groups dysfunctions by anatomical origin: hypothalamic (Type I), pituitary (Type II), ovarian (Type III), and PCOS (Type IV). These are further subtyped using the GAIN-FIT-PIE framework, which incorporates genetic, autoimmune, iatrogenic, neoplastic, functional, infectious, inflammatory, traumatic/vascular, physiological, idiopathic, and endocrine factors to guide precise and individualized treatment. Hormonal therapy remains the cornerstone for the management of menstrual disorders, with combined oral contraceptives (COCs) and progestogens widely used. Among progestogens, dydrogesterone offers distinct advantages. It is a retroprogesterone with high oral bioavailability and selective activity at progesterone receptors, devoid of androgenic, estrogenic, and glucocorticoid effects. This pharmacological profile makes it particularly suitable for patients with contraindications to estrogen-containing therapies, such as those with a history of migraine with aura or thrombophilia. Evidence from clinical trials supports the effectiveness of dydrogesterone in inducing withdrawal bleeding, regulating menstrual cycles, stabilizing the endometrium, and alleviating heavy menstrual bleeding and dysmenorrhea – all without suppressing ovulation. Its neutral effect on lipid metabolism, glucose homeostasis, and coagulation profile supports its use in women with cardiovascular risk or metabolic syndrome.

Dydrogesterone is an appropriate therapeutic option for women across all age groups, from adolescence to menopause. In patients with polycystic ovary syndrome (PCOS), it can be effectively used during intervals between COC cycles to maintain menstrual cycle regularity.

Conclusions: The reasonable and rational management of menstrual disorders should be guided by the underlying etiology, the patient's reproductive goals, and individual safety considerations. Dydrogesterone represents an effective and safe therapeutic option for a broad spectrum of menstrual disturbances.

Keywords: menstrual disorders; abnormal uterine bleeding (AUB); dydrogesterone; amenorrhea; ovulatory dysfunction; progesterone therapy

THIN ENDOMETRIUM: POTENTIAL OF ENZYME-BASED THERAPY

LALI PKHALADZE, MD, PhD; NINO DAVIDOVA, MD; NINO DATOSHVILI, MD
Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Thin endometrium, typically defined as an endometrial thickness of ≤ 7 mm during the late proliferative phase, is associated with poor reproductive outcomes. Its etiology is multifactorial, ranging from hormonal insufficiencies and iatrogenic injuries to chronic endometritis and impaired uterine perfusion.

Chronic endometritis (CE) is often underdiagnosed due to nonspecific symptoms. Frequently caused by pathogens such as *Mycoplasma*, *Ureaplasma*, or *Escherichia coli*, CE induces persistent inflammation, fibrosis, and angiogenic disruption, ultimately leading to an unresponsive and thin endometrial lining. These pathophysiologic changes are often compounded by excessive extracellular matrix (ECM) deposition, intrauterine adhesions, and the formation of microbial biofilms.

Current treatments for thin endometrium – including high-dose estrogen, pentoxifylline, vitamin E, granulocyte colony-stimulating factor (G-CSF), platelet-rich plasma (PRP), stem cell therapy, and antibiotics (in cases of CE) – have demonstrated limited efficacy, variable reproducibility, and are often cost-intensive.

Recent interest has focused on enzyme-based therapies that target microenvironmental alterations within the endometrium. Streptokinase, a bacterial-derived fibrinolytic enzyme, promotes the conversion of plasminogen to plasmin, facilitating fibrin degradation and reducing fibrotic tissue – thereby improving endometrial vascularity and pliability. Streptodornase is an enzyme capable of dissolving viscous nucleoprotein masses, dead cells, and pus without harming viable cells or disrupting physiological functions. It degrades extracellular DNA within biofilms, reducing chronic inflammation and promoting tissue remodeling.

Enzyme-based therapies have shown efficacy in conditions such as endometriosis, chronic pelvic inflammation, and adhesion prevention. Preliminary studies, including case series and pilot trials, have reported improved endometrial thickness, vascularity, and implantation rates following enzyme administration – particularly in cases related to CE and those that are hormone refractory.

While early findings are promising, large-scale randomized trials are required to confirm the efficacy of these therapies, optimize enzyme dosing, and explore potential combination strategies with regenerative treatments.

Keywords: thin endometrium; chronic endometritis; enzyme-based therapy; streptokinase; streptodornase

HORMONAL CORRECTION OF MENSTRUAL CYCLE DISORDERS (MCD): FOCUS ON SEX STEROIDS

GEORGE TEVDORASHVILI, MD, PhD;¹ MARIAMI ANDGULADZE, MD, PhD²

¹ Tbilisi State Medical University, First University Clinic, Tbilisi, Georgia

² Medicare Georgia, Tbilisi, Georgia

ABSTRACT

Context: Maintaining menstrual health plays a vital role in maintaining endocrine health function, reproductive and general health, and quality of life (QOL) in both adolescent girls and women of reproductive age.

Menstrual cycle disorders (MCDs), whose effects are not limited to women of reproductive age and lead to adverse health outcomes beyond reproductive age, significantly increases the burden of noncommunicable diseases for the general population worldwide.

Menstrual cycle disorders, their consequences, and the challenges of diagnosis, treatment, and future prospects vary across the reproductive stages of a woman's life, with differences in age, endocrine profile, demands, and risks.

Interventions: For the treatment of menstrual disorders, sex steroid hormonal medications are mainly used, both as monotherapy and in combination regimens.

Clinical challenges: The main challenges of the action of sex steroid drugs are the control of cycles and bleeding, the action on the central nervous system, and the control of urogenital and sexual changes. In some patients, the response to sex steroids is paradoxical.

It is important to carefully determine the selection of each of them, the choice of combined use, the route of administration, and the dosage regimen, as well as the duration of administration.

Future prospects: When making decisions regarding the choice of sex steroid hormones in the presence of menstrual cycle disorders (MCD), it is recommended to consider their impact on the overall quality of life, use an individualized approach for each patient, including the integration of pharmacogenetic characteristics, biomarkers, and artificial intelligence, and clearly define what, when, and how to use it to achieve the desired results – with minimized risks of side effects and complications.

Keywords: menstrual cycle disorders; sex steroids; hormonal therapy; reproductive health; quality of life; pharmacogenetics

მენსტრუალური ციკლის დარღვევების (MCD)

ჰორმონალური კორექცია:

ფოკუსირება სასქესო სტეროიდებზე

გიორგი თავდორაშვილი,¹ მარიამ ანდლულაძე²

¹ თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის პირველი საუნივერსიტეტო კლინიკა, თბილისი, საქართველო

² კლინიკა “მედიქა”, თბილისი, საქართველო

აბსტრაქტი

კონტექსტი: მენსტრუალური ჯანმრთელობის შენარჩუნება მნიშვნელოვან როლს თამაშობს როგორც მოზარდი გოგონების, ასევე, რეპროდუქციული ასაკის ქალების ენდოკრინული ფუნქციის, რეპროდუქციული და ზოგადი ჯანმრთელობისა და სიცოცხლის მაღალი ხარისხის (QOL) შენარჩუნების კუთხით.

მენსტრუალური ციკლის დარღვევები (MCD) კი, რომელთა ეფექტიც არ შემოიფარგლება ქალების მხოლოდ რეპროდუქციული ასაკით და იწვევს ჯანმრთელობის არასასურველი შედეგების განვითარებას რეპროდუქციული ასაკის მიღმა, მნიშვნელოვნად ზრდის არაგადამდები დაავადებების ტვირთს ზოგადი პოპულაციისთვის მთელს მსოფლიოში. მენსტრუალური ციკლის დარღვევები, მათი შედეგები და, როგორც დიაგნოსტიკისა თუ მკურნალობის, ასევე, სამომავლო პერსპექტივის გამოწვევები, განსხვავდება ქალის ცხოვრების რეპროდუქციული პერიოდების მიხედვით – სხვაობით ასაკში, ენდოკრინულ პროფილში, მოთხოვნასა და რისკებში.

ინტერვენციები: მენსტრუალური ციკლის დარღვევების სამკურნალოდ, უმეტესწილად, სასქესო სტეროიდული ჰორმონალური მედიკამენტები გამოიყენება, როგორც მონოთერაპიის, ასევე კომბინირებული სქემების სახით.

კლინიკური გამოწვევები: სასქესო სტეროიდული მედიკამენტების მოქმედების მთავარ გამოწვევებს ციკლებისა და სისხლდენის კონტროლი, მოქმედება ცენტრალურ ნერვულ სისტემაზე, ურო-გენიტალური და სექსუალური ცვლილებების კონტროლი წარმოადგენს. პაციენტების ნაწილში სასქესო სტეროიდებზე პასუხი პარადოქსულია. მნიშვნელოვანია თითოეული მათგანის შერჩევის, კომბინირებული გამოყენების შესახებ არჩევანის, მიღების გზისა და დოზირების რეჟიმის, ასევე მიღების ხანგრძლივობის ფრთხილი განსაზღვრა.

მომავლის პერსპექტივა: მენსტრუალური ციკლის დარღვევების (MCD) არსებობის დროს სასქესო სტეროიდული ჰორმონების არჩევასთან დაკავშირებით გადაწყვეტილების მიღებისას, რეკომენდებულია, გავითვალისწინოთ მათი გავლენა სიცოცხლის ზოგად ხარისხზე, გამოვიყენოთ ინდივიდუალიზებული მიდგომა თითოეული პაციენტისთვის, მათ შორის, ფარმაცოგენეტიკური მახასიათებლების, ბიომარკერებისა და ხელოვნური ინტელექტის ინტეგრაცია და მკაფიოდ განვსაზღვროთ თუ რა, როდის და როგორ გამოვიყენოთ სასურველი შედეგების მისაღწევად – გვერდითი ეფექტებისა და გართულებების განვითარების მინიმალიზებული რისკებით.

საკვანძო სიტყვები: მენსტრუალური ციკლის დარღვევები; სასქესო სტეროიდები; ჰორმონალური თერაპია; ენდოკრინული ჯანმრთელობა; ცხოვრების ხარისხი; ინდივიდუალიზებული მკურნალობა

THE HORMONAL TRIANGLE OF POLYCYSTIC OVARY SYNDROME (PCOS): FROM NEUROENDOCRINE FACTORS TO METABOLIC DISORDERS AND INFERTILITY

GEORGE TEVDORASHVILI, MD, PhD;¹ MARIAMI ANDGULADZE, MD, PhD²

¹ Tbilisi State Medical University, First University Clinic, Tbilisi, Georgia

² Medicare Georgia, Tbilisi, Georgia

ABSTRACT

Context: Polycystic ovary syndrome (PCOS) is a significant public health problem – a complex and heterogeneous endocrine disease that affects women of reproductive age and is characterized by the triad of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology.

Objective: This review explores the concept of the “hormonal triangle” of PCOS – an interconnected network that includes the hypothalamic-pituitary-ovarian (HPO) axis, the relationship between insulin resistance and metabolic dysfunction, and the resulting impact on fertility.

Methods: We review neuroendocrine disorders, particularly the role of GnRH pulsatility, LH/FSH imbalance, and altered feedback loops; metabolic outcomes, such as insulin resistance, obesity, and their contribution to anovulation and hyperandrogenism; and reproductive outcomes, including chronic anovulation, endometrial dysfunction, and infertility.

Conclusions: Understanding the dynamic interactions between these systems is crucial for the development of personalized treatment strategies, including hormonal, metabolic, and lifestyle interventions. The review also highlights the need for new studies on biomarkers and therapeutic targets for personalized management of polycystic ovary syndrome (PCOS).

Keywords: polycystic ovary syndrome; neuroendocrine factors; insulin resistance; infertility; metabolic disorders; hypothalamic-pituitary-ovarian axis

პოლიკისტოზური საკვარცხების სინდრომი (PCOS) არის საზოგადოებრივი პოლიკისტოზური საკვარცხების სინდრომის (PCOS) ჰორმონალური სამკურნალო: ნეიროენდოკრინული ფაქტორებიდან მეტაბოლურ დარღვევებსა და უნაყოფოობამდე

ბიორბი თავდორაშვილი;¹ მარიამ ანდლულაძე²

¹ თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის პირველი საუნივერსიტეტო კლინიკა, თბილისი, საქართველო

² კლინიკა “მედიქა”, თბილისი, საქართველო

აბსტრაქტი

კონტექსტი: პოლიკისტოზური საკვარცხების სინდრომი (PCOS) არის საზოგადოებრივი ჯანმრთელობის მნიშვნელოვანი პრობლემა – რთული და ჰეტეროგენული ენდოკრინული დაავადება, რომელიც აზიანებს რეპროდუქციული ასაკის ქალებს და ხასიათდება ჰიპერანდროგენიზმის, ოვულაციური დისფუნქციის და პოლიკისტოზური საკვარცხების მორფოლოგიის ტრიადით.

მიზანი: ეს მიმოხილვა იკვლევს PCOS-ის “ჰორმონალური სამკურნალო” კონცეფციას – ურთიერთდაკავშირებულ ქსელს, რომელიც მოიცავს ჰიპოთალამო-ჰიპოფიზ-საკვარცხების (HPO) დერძს, ინსულინრეზისტენტობასა და მეტაბოლურ დისფუნქციას შორის კავშირს და შედეგად მიღებულ გავლენას ნაყოფიერებაზე.

მეთოდები: ჩვენ განვიხილავთ ნეიროენდოკრინულ დარღვევებს, განსაკუთრებით, GnRH პულსაციის როლს, LH/FSH დისბალანსს და შეცვლილ უკუკავშირის მარყუქებს; მეტაბოლურ შედეგებს, როგორიცაა ინსულინრეზისტენტობა, სიმსუქნე და მათი წვლილი ანოვულაციასა და ჰიპერანდროგენიზმში; რეპროდუქციულ შედეგებს, მათ შორის ქრონიკულ ანოვულაციას, ენდომეტრიუმის დისფუნქციას და უნაყოფოობას.

დასკვნები: ამ სისტემებს შორის დინამიური ურთიერთქმედების გაგება გადამწყვეტია პერსონალიზებული მკურნალობის სტრატეგიების შემუშავებისთვის, მათ შორის ჰორმონალური, მეტაბოლური და ცხოვრების წესის ჩარევების ჩათვლით.

მიმოხილვაში ასევე ხაზგასმულია ბიომარკერებისა და თერაპიული მიზნების შესახებ ახალი კვლევების საჭიროების როლი პოლიკისტოზური საკვარცხების სინდრომის (PCOS) პერსონალიზებული მენეჯმენტისთვის.

საძიებო სიტყვები: პოლიკისტოზური საკვარცხების სინდრომი; ნეიროენდოკრინული დარღვევები; ინსულინრეზისტენტობა; მეტაბოლური დარღვევები; უნაყოფოობა; პერსონალიზებული მკურნალობა



THE BUSINESS IN COMBINATION WITH SCIENCE

The pharmaceutical company GEA was founded in 1995 and has been successfully operating in the South Caucasus region (Georgia, Armenia, and Azerbaijan) in the import, distribution, and introduction of products.



IRINA TCHELIDZE

The founder of pharmaceutical company "Gea"
President of Pharmaceutical Companies Association in Georgia



KHATUNA MANJGALADZE

The founder of pharmaceutical company "Gea"

The pharmaceutical company GEA provides a complete chain of services from the selection of the drug to its sale:

Today, Gea is an official partner and distributor of more than 45 pharmaceutical factories in the Transcaucasian region.

The company's portfolio includes more than 400 of medicines, biologically active supplements, disposable surgical consumables, and cosmetics.

- More than 45 partner pharmaceutical companies from 15 countries
- 400+ pharmaceutical products
- 170+ employees (marketing team in all three countries: Georgia, Armenia, Azerbaijan)
- 24+ local distributors (Georgia, Armenia, Azerbaijan)
- 90%+ female employees.

COMPANY PHILOSOPHY

- "GEA" takes responsibility for patients, doctors, and all consumers who use the products it imports.
- Honest and stable relations with partners are of the utmost importance for "GEA"
- "GEA" aims to supply the medical field in the Transcaucasian region with products that meet the highest quality standards and improve the quality of life of the population.
- The health of each user is of the most important for "GEA" It is aimed at maintaining consistently high-quality service. "GEA"'s highly qualified specialists constantly collect and analyze pharmacovigilance information from doctors and patients and provide this information to manufacturers.
- "GEA" provides a safe and desirable working environment for employees and permanently takes care of their professional growth. Relations in the company are based on ethical principles
- "GEA" 's constant pursuit of quality improvement allows each of its employees to be involved in continuous education and development processes, which are in full compliance with international European standards
- "GEA" stands out for its high responsibility towards the society in which it exists and operates. The company is actively involved in social projects.

EFFICACY OF COMBINED SURGICAL AND HORMONAL THERAPY FOR INFERTILE PATIENTS WITH DEEP ENDOMETRIOSIS

DAVID SKHIRTADZE, MD, MPH, PhD;¹ JENARO KRISTESASHVILI, MD, PhD;²
RAMAZ CHAREKISHVILI, MD, PhD¹

¹ Department of Endoscopic Gynecologic Surgery, Clinic "Caraps Medline", Tbilisi, Georgia

² Faculty of Medicine, Department of Obstetrics, Gynecology, and Reproductology, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: Although laparoscopic surgery is effective for treating deep endometriosis (DE), postoperative management remains controversial. Dienogest therapy after surgery may improve spontaneous pregnancy rates and reduce endometriosis-associated pain severity.

Objective: To determine the efficacy of combined surgical and hormonal therapy in infertile patients with DE.

Materials and Methods: An open-label, randomized controlled trial was conducted among 88 women aged 21-38 years with infertility who underwent surgery for DE. After surgery, eligible patients were randomly assigned to two groups. Group 1 (n = 44) received dienogest for 3 months postoperatively, and Group 2 (n = 41) received no postoperative treatment. Three patients were lost to follow-up. The primary outcome was the pregnancy rate nine months after surgery. Secondary outcomes included mean dysmenorrhea and chronic pelvic pain (CPP) intensity, assessed before and nine months after surgery.

Results: No statistically significant differences were observed between groups in terms of age, preoperative dysmenorrhea and CPP scores, distribution of endometriosis phenotypes (isolated DE, superficial peritoneal disease, endometriomas), or pelvic adhesions ($p > 0.05$). Group 1 had a significantly higher pregnancy rate than Group 2 (47.7% vs 22.0%, $p = 0.013$). Group 1 also showed greater reductions in mean dysmenorrhea scores (2.8 vs 5.63, $p < .001$) and CPP scores (2.7 vs 3.4, $p < .001$).

Conclusions: Combined surgical and hormonal therapy is significantly more effective than surgery alone in improving fertility outcomes and alleviating pelvic pain in patients with DE.

Keywords: deep endometriosis; infertility; dysmenorrhea; chronic pelvic pain; dienogest

HOMOCYSTEINE LEVELS IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME (PCOS) WITH AND WITHOUT INSULIN RESISTANCE

MANANA URJUMELASHVILI, MD;¹ JENARO KRISTESASHVILI, MD, PhD;² EKA ASANIDZE, MD³

¹ PhD Assistant Professor, Faculty of Medicine, University Geomedi, Tbilisi, Georgia

² Prof. Professor, Department of Obstetrics, Gynecology, and Reproductology, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

³ PhD Associate Professor, Faculty of Medicine, University Geomedi, Tbilisi, Georgia

ABSTRACT

Introduction: In recent years, it is considered that hyperhomocysteinemia (Hhcy), which may be associated with insulin resistance, plays an important role in the pathogenesis of PCOS.

Aim of the study: The aim of the study was to evaluate homocysteine (Hcy) levels in patients with PCOS with and without insulin resistance.

Materials and methods: The study was conducted in 59 patients with PCOS aged 13-35 (mean age 24.5 ± 3.5). Patients were divided into two groups: Group I – 38 patients with PCOS and insulin resistance, and Group II – 21 patients with PCOS without insulin resistance. Along with investigations, which were conducted for the diagnosis of PCOS, homocysteine levels were measured (ref. values $5 - 10.5 \mu\text{mol/l}$). According to homocysteine values, PCOS patients were divided into three subgroups: low $\leq 6.09 \mu\text{mol/l}$, moderate $6.10 - 9.33 \mu\text{mol/l}$, and high $> 9.34 \mu\text{mol/l}$.

Results: The mean level of homocysteine was significantly higher in group I compared to group II (group I mean Hcy- 14.6 mg/l , group II – 9.2 mg/l) ($P < 0.001$). After dividing the homocysteine levels into three subgroups (low, moderate, high) it was determined that in PCOS patients with insulin resistance increased and high normal levels of homocysteine ($> 9.34 \mu\text{mol/l}$) were detected in 84% of cases ($n=32$), moderate – in 11% ($n=4$), low – in 5% ($n=2$). In patients without insulin resistance, these indicators were respectively: high – in 52% ($n=11$) ($P < 0.05$), moderate – in 38% ($n=8$) ($P < 0.05$), low – in 10% ($n=2$) ($P > 0.05$).

Conclusion: Homocysteine level is significantly elevated in patients with PCOS and insulin resistance compared to patients without insulin resistance. In the management of patients with PCOS, along with correction of insulin resistance, control and correction of homocysteine level should be considered, which will improve their reproductive outcome.

Keywords: PCOS, homocysteine, hyperhomocysteinemia, insulin resistance, RPL, infertility

INSULIN RESISTANCE AND HYPERHOMOCYSTEINEMIA AS RISK FACTORS FOR RECURRENT PREGNANCY LOSS IN POLYCYSTIC OVARY SYNDROME

SHORENA TCHIOKADZE, PhD Student;¹ **ELENE ASANIDZE**, PhD Student;²
JENARO KRISTESASHVILI, MD, PhD³

¹ David Tvildiani Medical University, Tbilisi, Georgia

² University Geomedi, Tbilisi, Georgia

³ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: Pregnancy loss is a common and distressing complication for women with polycystic ovary syndrome (PCOS). Metabolic and hormonal abnormalities in PCOS, including insulin resistance and hyperandrogenism, are thought to contribute to recurrent pregnancy loss (RPL). Additionally, hyperhomocysteinemia (Hhcy) is recognized as a risk factor for thrombosis and fetoplacental insufficiency, both of which can complicate pregnancy. Despite emerging evidence linking these factors to RPL, the exact roles of insulin resistance and hyperhomocysteinemia in the pathogenesis of pregnancy loss in PCOS patients remain unclear.

Objective: The aim of the study was to investigate the role of hyperhomocysteinemia and insulin resistance and explore their correlation in PCOS patients with recurrent pregnancy loss.

Materials and Methods: A case-control study was conducted with 130 Georgian women under 30 years old, diagnosed with PCOS according to the Rotterdam criteria. Participants were divided into two groups: 70 with a history of RPL (study group) and 60 with live births (control group). The RPL group was further subdivided based on HOMA-IR: with (n=38) and without (n=32) insulin resistance. Hormonal and ultrasound assessments were performed during the early follicular phase. RPL was defined as two or more clinical spontaneous abortions.

Results: The average homocysteine level and insulin resistance in PCOS patients with RPL were significantly higher than in controls ($p<0.05$). Insulin resistance and hyperhomocysteinemia were more prevalent in the RPL group (70% and 56%, respectively) compared to controls (54.3% and 9.4%, $p<0.05$). Homocysteine levels were significantly higher in RPL patients with insulin resistance compared to those without ($p<0.05$). No significant differences were found in AMH, LH, FSH, testosterone, or ovarian reserve between subgroups. In the RPL group, a

significant positive correlation was observed between homocysteine, HOMA-IR, BMI, AMH, and FT levels ($p < 0.05$).

Conclusions: Hyperhomocysteinemia and insulin resistance may significantly contribute to recurrent pregnancy loss in women with PCOS. These findings highlight the need for further investigation into their roles in the pathophysiology of RPL.

Keywords: polycystic ovary syndrome; recurrent pregnancy loss; insulin resistance; hyperhomocysteinemia; metabolic risk factors

EFFECT OF INTRAOPERATIVE LIDOCAINE INJECTION ON POSTOPERATIVE PAIN AND RECOVERY IN ENDOMETRIAL CANCER PATIENTS UNDERGOING LAPAROSCOPICALLY ASSISTED VAGINAL HYSTERECTOMY WITH ICG SLN MAPPING

MARIKA JAPARIDZE, MD, PhD

Onco-gynecologist, Head of the Gynecological Department, Aversi Clinic, Tbilisi, Georgia

ABSTRACT

Background: Laparoscopic hysterectomy with SLN lymphadenectomy using ICG tracer is a recommended standard in low- and intermediate-risk early-stage endometrial cancer patients. Since the implementation of laparoscopy in onco-gynecology, many studies have demonstrated advantages over traditional open surgery. Reduced postoperative pain is one of the key priorities of laparoscopy. However, post-surgical rehabilitation processes and quality of life in oncological patients undergoing pelvic lymphadenectomy remain subjects of interest. We used a laparoscopically assisted vaginal hysterectomy as a modification to inject lidocaine into the uterosacral ligaments before cutting the vaginal cuff and performing vaginal extraction to evaluate postoperative pain.

Objective: To evaluate the impact of intraoperative lidocaine injection into the uterosacral ligaments on postoperative pain and recovery in patients undergoing laparoscopically assisted vaginal hysterectomy (LAVH) with indocyanine green (ICG) sentinel lymph node (SLN) mapping for early-stage low- and intermediate-risk endometrial cancer.

Methods: A prospective comparative study was conducted on 140 patients with early-stage endometrial cancer undergoing LAVH with ICG SLN mapping and lymphadenectomy. Patients were randomly assigned to two groups (n = 70 each). In the intervention group, 10 mL of 1% lidocaine was injected into both uterosacral ligaments prior to vaginal cuff incision and uterine extraction (after laparoscopic ICG lymphadenectomy and uterine immobilization were completed). The control group underwent the same procedure without lidocaine injection. Postoperative pain was assessed 4 hours after surgery using the Visual Analogue Scale (VAS). Postoperative recovery time and length of hospital stay were recorded.

Results: The mean VAS score at 4 hours postoperatively in the lidocaine group was 3.9 compared with 5.85 in the control group, indicating lower reported pain in the lidocaine group. Patients in the lidocaine group also demonstrated faster postoperative recovery, enabling discharge in <30 hours postoperatively in most cases, compared with an average hospital stay of 48 hours in the control group. No lidocaine-related adverse events were observed.

Conclusions: Intraoperative lidocaine injection into the uterosacral ligaments significantly reduces early postoperative pain and facilitates faster recovery in patients undergoing LAVH with ICG SLN mapping for early-stage endometrial cancer. This simple, low-cost technique, used as an innovative method in this study, may improve patient comfort and shorten hospital stays. Further studies with complete statistical analysis are warranted.

Keywords: endometrial cancer; laparoscopically assisted vaginal hysterectomy; lidocaine; post-operative pain; recovery time

FOLLICULAR VARIANT OF PAPILLARY THYROID MICROCARCINOMA ARISING IN STRUMA OVARIII: A RARE CASE REPORT

NUTSA CHIGHLADZE, Resident
Medicare Georgia, Tbilisi, Georgia

ABSTRACT

Background: Struma ovarii is a rare ovarian teratoma composed predominantly of thyroid tissue, with malignant transformation observed in only 5-10% of cases. Among these, papillary thyroid carcinoma (PTC) is the most common histological subtype. However, the follicular variant of papillary thyroid microcarcinoma (FVPTC) arising in struma ovarii is scarce, with few documented cases worldwide. Diagnosis is difficult due to subtle histological features and its often-indolent clinical course.

Objective: To present a rare case of FVPTC arising in struma ovarii in a young woman, emphasizing diagnostic findings, surgical management, and follow-up strategies.

Materials and Methods: We retrospectively reviewed the clinical data of a 29-year-old woman who underwent laparoscopic ovarian cystectomy. Preoperative evaluation included pelvic ultrasound, tumor marker screening (CEA, CA 125, CA 19-9), and histopathological examination. The patient had a history of parathyroid adenoma resection four months prior; this information was considered separately during endocrine evaluation.

Results: A 40×50 mm right ovarian cyst was incidentally detected on routine ultrasound. Doppler ultrasound showed increased vascularization. Tumor markers were within normal limits. Laparoscopic cystectomy was performed. Histopathological analysis revealed struma ovarii with a follicular variant of papillary thyroid microcarcinoma, confined to the ovary without capsular or vascular invasion. Chest CT and abdominal/pelvic MRI showed no abnormalities. The thyroid gland appeared normal on imaging and remained disease-free during follow-up. A multidisciplinary team recommended conservative management without adnexectomy, thyroidectomy, or radioiodine therapy. Serial gynecologic and endocrine follow-up showed no signs of recurrence.

Conclusions: This case highlights the rarity of FVPTC arising in struma ovarii. Conservative treatment was chosen due to confined localization, absence of invasion, and normal thyroid findings. Although no recurrence has been observed so far, long-term follow-up is necessary to assess the safety and adequacy of non-radical management in such rare cases.

Keywords: struma ovarii; follicular variant; papillary thyroid carcinoma; conservative management

კომპანია ოვამედი ამერიკული ჰოლდინგის CooperSurgical-ის ექსკლუზიური წარმომადგენელია საქართველოსა და აზერბაიჯანში, რომელიც მსოფლიო ლიდერია ქალთა რეპროდუქციული ჯანმრთელობის მიმართულებით და სანდო პარტნიორია მსოფლიოს ყველა ქვეყანაში. ოვამედი 2012 წლიდან ამარაგებს არსებულ ინ ვიტრო განაყოფიერების ლაბორატორიებსა და კლინიკებს. Cooper Surgical-ის გარდა ოვამედი Cryos International-ის და სხვადასხვა კომპანიების წარმომადგენელია.

ოვამედი არის წამყვანი ქართული კომპანია, რომელიც სპეციალიზდება ამ სფეროსთვის მაღალხარისხიანი სამედიცინო და სახარჯო მასალის დისტრიბუციაში. ბაზარზე 13 წლიანი გამოცდილებით ოვამედი სანდო და სტაბილური პარტნიორია ყველა ინ ვიტრო განაყოფიერების კლინიკისათვის. ის აქტიურად თანამშრომლობს ქვეყნის მასშტაბით კლინიკებთან და ლაბორატორიებთან, რათა მიაწოდოს მათ თანამედროვე რეპროდუქციული ტექნოლოგიებისთვის საჭირო ინოვაციები და სამეცნიერო კვლევები სხვადასხვა საკითხებზე.

ოვამედის გუნდი გამოირჩევა პროფესიონალიზმით, ხარისხზე ორიენტირებითა და საიმედო მომსახურებით. კომპანია თავის პარტნიორებს, არა მარტო უმაღლესი ხარისხის პროდუქციას, არამედ პროფესიონალურ კონსულტაციას, სამედიცინო აპარატურის სერვისს, მონიტორინგსა და გრძელვადიან მხარდაჭერას სტავაზობს. გარდა ამისა კომპანია ოვამედი მუდმივად ზრუნავს საქართველოში და აზერბაიჯანში მოდერნული ექიმებისა და რეპროდუქტოლოგების პროფესიულ განვითარებაზე და ორგანიზებას უწევს მათ მონაწილეობას სხვადასხვა ტრენინგებსა და სასწავლო პროგრამებზე როგორც საქართველოში ასევე ევროპის სხვადასხვა ქვეყნებში. გლობალური და ადგილობრივი გამოცდილების შერწყმით, კომპანია ოვამედს მნიშვნელოვანი წვლილი შეაქვს რეპროდუქციული მედიცინის განვითარებაში საქართველოში.

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მპს ოვამედი; ა. შანიძის 13, 0179 თბილისი, საქართველო;

ტელ: +995322 18 05 70; მისამართი: ელ ფოსტა: ovamed@gmail.com

Ovamed ltd; Shanidze str: N 13, 0179 Tbilisi, Georgia;

Tel: +995322 18 05 70; E-mail: ovamed@gmail.com

MICROWAVE ABLATION OF UTERINE FIBROIDS

NINO DZNELASHVILI, MD

*Department of Obstetrics and Gynecology, David Tvildiani Medical University
"AIETI" Medical School, Tbilisi, Georgia*

ABSTRACT

Background: In modern gynecology, the diagnosis and treatment of uterine fibroids have not lost their importance due to the high frequency of the disease, primarily in women of reproductive age. The severe symptoms of the disease, the complication of reproductive function realization, and the negative impact on the patient's health and quality of life make it clinically significant. Uterine myoma is most often found in women of reproductive age, and due to uterine fibroids, approximately 41-74% of gynecological operations are performed annually.

Objective: According to various authors, female infertility, spontaneous abortion, and premature birth are associated with uterine myoma. In modern gynecology, we often encounter the "rejuvenation" of uterine fibroids. This has become the basis for the development and implementation of organ-preserving treatment methods for this disease.

Materials and Methods: Nowadays, choosing the correct and timely method of treating uterine fibroids is considered a great challenge for gynecologists. One of the modern minimally invasive treatment methods is microwave ablation of uterine fibroids under ultrasound guidance. The value of this method lies in its high clinical effectiveness.

Results: Microwave ablation is an organ-preserving procedure that prevents damage to the structures of the pelvic organs. After ablation, the pathological areas are reduced in size, leading to the immediate disappearance of clinical symptoms. It does not affect the normal functioning of the ovaries or change the receptor apparatus of the endometrium. The procedure can be performed via transdermal, transvaginal, or laparoscopic approaches, with fast and painless rehabilitation. Follow-up examinations performed after 1, 3, and 5 months showed that the nodule had decreased in size by 30%.

Conclusions: Considering the prevalence of uterine fibroids in the young population who have not yet completed their reproductive goals, the uncontrolled nature of their growth, and their significant impact on quality of life, I believe that immediately after the diagnosis of uterine fibroids, the presence of myoma should not be ignored, and an effective treatment strategy tailored to the patient's condition and reproductive plans should be selected in a timely manner.

Keywords: myoma; uterus; microwave ablation; myomectomy

POSTOPERATIVE MANAGEMENT OF HYSTEROSCOPIC METROPLASTY FOR PATIENTS WITH SEPTATE AND T-SHAPED UTERUS

**IRAKLI SIMONIA, MD;¹ JENARO KRISTESASHVILI, MD, PhD;² MARIKA JAPARIDZE, MD;³
DAVIT SKHIRTADZE, MD¹**

¹ Ivane Javakhishvili Tbilisi State University, Faculty of Medicine, Department of Obstetrics, Gynecology, and Reproductology, Tbilisi, Georgia

² Ivane Javakhishvili Tbilisi State University, Faculty of Medicine, Department of Obstetrics, Gynecology, and Reproductology; Clinic "Universe", Tbilisi, Georgia³ Aversi Clinic, Tbilisi, Georgia

ABSTRACT

Background: The successful implantation of the embryo and normal development of pregnancy after hysteroscopic metroplasty in women with congenital uterine anomalies requires a normal endometrium. This condition must be achieved by preventing the development of postoperative intrauterine adhesions (IUA) and stimulating endometrium regeneration. Despite years of studies evaluating strategies to prevent IUA after operative hysteroscopy, it is still unclear which strategies are most effective.

Objectives: The study aimed to evaluate the efficacy of hormone treatment, barrier gel, and their combined application following hysteroscopic metroplasty in women with septate (U2) and T-shaped uteri (U1a).

Material and Methods: Hysteroscopic uterine septum resection was performed in 236 patients with U2, while lateral metroplasty was conducted in 191 patients with U1a. After surgery, 56 women with U2 and 58 women with U1a received hormone therapy (HT). Cross-linked hyaluronic acid (cHA) gel was applied to 54 women with U2 and 37 with U1a. Combined therapy (CT) using both HT and cHA gel was implemented for 48 women with U2 and 33 with U1a. Postoperative treatment was not performed in the corresponding control groups. Reproductive outcomes were evaluated within 18 ± 6 months postoperatively.

Results: Compared to the control group, the clinical pregnancy rate was significantly higher in the U2-HT, U2-cHA, and U2-CT groups and the U1a-HT and U1a-CT groups ($p < 0.05$). The miscarriage rate was significantly lower in the U2-cHA and U2-CT groups ($p < 0.05$). The live birth rate was significantly higher in the U2-cHA and U2-CT groups ($p < 0.05$). A second-look hysteroscopy revealed intrauterine adhesions in U2-HT (9%) and its respective control group (33%), as well as in the U1a control group (18%).

Conclusion: Hysteroscopic metroplasty enhances reproductive outcomes in women with septate and T-shaped uteri. Postoperative treatment is necessary to prevent the development of intrauterine adhesions.

Keywords: hysteroscopic metroplasty; intrauterine adhesions; congenital uterine anomalies; septate uterus; T-shaped uterus; reproductive outcomes

FERTILITY-SPARING MANAGEMENT IN EARLY-STAGE ENDOMETRIAL CANCER: PATIENT SELECTION AND ONCOLOGIC CONSIDERATIONS

ZAZA TSITSISHVILI, MD, PhD

Department of Gynecology, American Hospital Tbilisi, Tbilisi, Georgia

ABSTRACT

Background: Endometrial cancer is the most common gynecologic malignancy in developed countries, and its rising incidence in women of reproductive age has driven interest in fertility-sparing management. Careful patient selection is essential to balance oncologic safety with reproductive goals.

Objective: To outline evidence-based criteria for identifying candidates for fertility-sparing treatment in early-stage endometrial cancer, based on ESGO/ESTRO/ESP guidelines and contemporary literature.

Methods: A review of guidelines and clinical studies was performed, focusing on histology, staging, imaging, lymph-node assessment, and patient factors influencing eligibility for conservative management.

Results: Fertility-sparing therapy is appropriate only for patients with grade 1 (well-differentiated) endometrioid adenocarcinoma, confined to the endometrium or showing <50% myometrial invasion (FIGO stage IA). No lymph-vascular space invasion should be present, and pelvic MRI or ultrasound must confirm the absence of deep invasion or extra-uterine disease. Sentinel lymph node (SLN) mapping is increasingly recommended to exclude occult nodal spread. Candidates should be younger women who desire future fertility, fully understand the risks, and commit to strict follow-up, including endometrial sampling every 3-6 months and definitive surgery after childbearing.

Conclusion: Stringent selection – integrating pathology, imaging, and SLN staging – ensures that fertility-sparing management remains a safe, feasible option for appropriately chosen patients.

Keywords: endometrial neoplasms; fertility preservation; conservative treatment; patient selection; lymphatic mapping; magnetic resonance imaging



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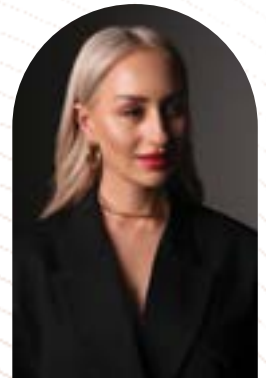
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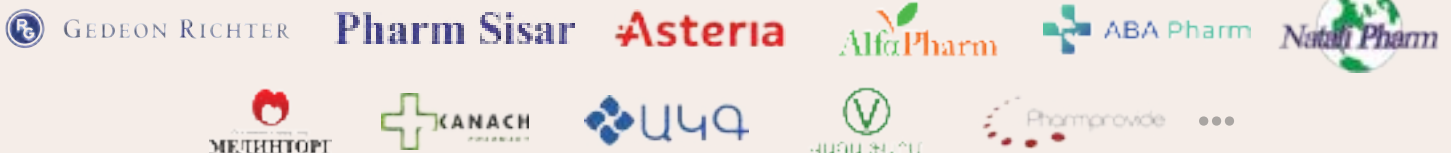
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GENETIC ASPECTS OF MALE INFERTILITY

MARIAM CHIPASHVILI, MD, PhD^{1,2,3}

¹ Tbilisi State University, Tbilisi, Georgia;

² Zhordania Medical Center, Tbilisi, Georgia;

³ Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Context: Male infertility affects approximately 7% of the global male population and contributes to nearly half of all infertility cases among couples. While environmental and lifestyle factors play a role, genetic abnormalities are increasingly recognized as critical determinants of impaired spermatogenesis.

Objective: To synthesize current knowledge on the genetic underpinnings of male infertility, evaluate emerging diagnostic technologies, and explore their implications for personalized reproductive medicine.

Methods: A comprehensive review of recent literature and genetic studies was conducted, with emphasis on chromosomal anomalies, Y chromosome microdeletions, and monogenic disorders. The diagnostic yield and clinical utility of next-generation sequencing (NGS) and whole-exome sequencing (WES) were assessed.

Results: Genetic abnormalities – including chromosomal aneuploidies, AZF region microdeletions, and pathogenic variants in genes regulating spermatogenesis – are associated with diverse phenotypes ranging from azoospermia to asthenozoospermia. WES has enabled the identification of novel candidate genes and refined genotype-phenotype correlations. A substantial proportion of cases remain idiopathic, particularly in populations with limited access to advanced genetic testing.

Conclusion: Genetic evaluation is pivotal for accurate diagnosis, prognosis, and counselling in male infertility. The integration of genomic technologies into routine clinical practice holds promise for improving diagnostic precision and informing therapeutic strategies. Future research should prioritize the characterization of ethnic and population-specific variants and the development of standardized genetic testing protocols.

Keywords: infertility, male/genetics; spermatogenesis/genetics; Y chromosome; chromosome deletion (AZF microdeletions); exome sequencing; high-throughput nucleotide sequencing; azoospermia/genetics; asthenozoospermia/genetics; genetic counseling

მამაკაცის უნაყოფობის გენეტიკური ასპექტები

მარიამ ჭიკაშვილი, MD, PhD^{1,2,3}

¹ მედიცინის დოქტორი, ექიმი-გენეტიკოსი თბილისის სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო

² ჟორდანიას სამედიცინო ცენტრი, თბილისი, საქართველო

³ ქართულ გერმანული რეპროდუქციული ცენტრი, თბილისი, საქართველო

აბსტრაქტი

კონტექსტი: მამაკაცის ფაქტორით გამოწვეული უნაყოფობა აღენიშნება მსოფლიოს მამრობითი სქესის მოსახლეობის 7%-ს, წყვილთა შორის კი დაახლოებით 50%-ს შეადგენს. ბოლო პერიოდში სპერმატოგენეზის დარღვევის მიზეზთა შორის, მნიშვნელოვნად გაიზარდა გენეტიკური ფაქტორების როლი.

კვლევის მიზანი: მამაკაცის უნაყოფობის შესახებ არსებული ინფორმაციის და თანამედროვე ტექნოლოგიების მნიშვნელობის შეფასება, მათი გავლენის შესწავლა პერსონალიზირებული სამედიცინო მიდგომის მიზნით.

კვლევის მეთოდები: მამაკაცის უნაყოფობის მქონე პაციენტს ჩაუტარდა გენეტიკური კვლევები: ციტოგენეტიკური კვლევა, Y ქრომოსომის მიკროდელეციის სკრინინგი, მონოგენური დაავადებების კვლევა. შეფასდა შემდგომი თაობის სექვენირების და მთლიანი ეგზომის სექვენირების დიაგნოსტიკური და კლინიკური მნიშვნელობა. ჩატარდა ბოლო პერიოდის სამეცნიერო ლიტერატურის მიმოხილვა.

კვლევის შედეგები: გენეტიკური ანომალიები, მათ შორის ქრომოსომული ანეუპლოიდიები, AZF უბნის მიკროდელეცია და სპერმატოგენეზის მარეგულირებელი პათოგენური ვარიანტების არსებობა უკავშირდება ვარიანტულ ფენოტიპურ გამოვლინებას აზოოსპერმიიდან ასტენოზოოსპერმიამდე. მთლიანი ეგზომის სექვენირება საშუალებას იძლევა გამოვლინდეს ახალი კანდიდატი გენები და დაიხვეწოს გენოტიპ-ფენოტიპის კორელაციები. მიუხედავად ამისა, შემთხვევათა დიდი ნაწილი კვლავ იდუმალიყოფად ითვლება, განსაკუთრებით იმ შემთხვევაში, როდესაც შეზღუდულია გენეტიკური კვლევის ჩატარება.

დასკვნა: გენეტიკური კვლევები მნიშვნელოვანია მამაკაცის უნაყოფობისას სწორი დიაგნოსტიკის, პროგნოზის განსაზღვრის და კონსულტირების მიზნით. გენეტიკური ტექნოლოგიების ინტეგრირება კლინიკურ პრაქტიკაში გააუმჯობესებს დიაგნოსტიკის შესაძლებლობებს და მართვის სტრატეგიას. შემდგომი კვლევების პრიორიტეტი ფოკუსირებული უნდა იყოს ეთნიკური და პოპულაციისთვის სპეციფიკური ვარიანტების განსაზღვრაზე და გენეტიკური ტესტირების პროტოკოლების შემუშავებაზე.

საკვანძო სიტყვები: მამაკაცის უნაყოფობა/გენეტიკა; სპერმატოგენეზი/გენეტიკა; Y ქრომოსომა; ქრომოსომული დელეცია (AZF მიკროდელეციები); ეგზომის სექვენირება; მაღალი გამტარუნარიანი სექვენირება (NGS); აზოოსპერმია/გენეტიკა; ასტენოზოოსპერმია/გენეტიკა; გენეტიკური კონსულტაცია.

REPRODUCTIVE GENETIC ADVANCES: SOLUTIONS OR NEW CHALLENGES?

MARIAM CHIPASHVILI, MD, PhD;^{1,2} MAKH JORBENADZE, MD, PhD;^{1,2}

SOPO KVALIASHVILI, MD, PhD;¹ JENARO KRISTESASHVILI, MD, PhD;² NANA KURASHVILI, MD^{1,2}

¹ Zhordania Medical Center, Tbilisi, Georgia

² Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: Recent innovations in reproductive genetics – such as expanded carrier screening (ECS), noninvasive prenatal testing (NIPT), and infertility panels – have become routine in clinical practice. These tools offer unprecedented opportunities for early risk assessment, personalized reproductive planning, fertility preservation, and pregnancy management.

Objective: To critically evaluate whether these technological advances provide definitive solutions to reproductive challenges or introduce new ethical and clinical complexities.

Materials and Methods: Expanded carrier screening, male and female infertility panels, whole-exome sequencing (WES), and NIPT were provided following thorough genetic counseling.

Results: Expanded carrier screening enables broader identification of at-risk couples, facilitating informed reproductive decisions – whether through assisted reproductive technology (ART) or spontaneous conception followed by prenatal genetic testing. IVF has expanded fertility options, particularly for patients with diminished ovarian reserve. WES is helpful in cases of unexplained infertility, family history of undiagnosed disorders, or suspected hereditary conditions. However, variants of uncertain significance (VUS) remain a significant obstacle: although some may underlie clinical symptoms, limited data restrict diagnostic certainty. Multidisciplinary collaboration is essential for accurate interpretation and patient management. NIPT offers safer and earlier fetal genetic screening, reducing reliance on invasive procedures. Yet its application must be guided by a comprehensive personal and family history, as well as a detailed ultrasound profile. False positives – especially in screening for autosomal aneuploidies and structural anomalies – underscore the need for confirmatory testing and cautious use.

Conclusion: Reproductive genetic technologies hold transformative promise but also pose significant challenges. Responsible clinical integration requires multidisciplinary teamwork, strong ethical standards, and culturally sensitive counseling. As reproductive genetics continues to evolve, each advancement must be met with thoughtful reflection, regulation, and rigorous implementation.

Keywords: reproductive genetics; infertility panel; expanded carrier screening; assisted reproductive technologies; whole exome sequencing; noninvasive prenatal testing

PREVALENCE AND DISTRIBUTION OF HIGH-RISK HPV GENOTYPES AMONG WOMEN WITH CYTOLOGICAL ABNORMALITIES IN GEORGIA

TAMAR DIDBARIDZE, MD, PhD, Prof.;¹ **SHORENA TCHIOKADZE, MD, PhD;**²
MAIA JANELIDZE, MD, PhD;³ **IVLIANE SURMAVA, MD;**⁴ **BACHANA APTSIAURI, MD**⁴

¹ Head of Department, Department of Microbiology, Tbilisi State Medical University, Tbilisi, Georgia

² Head of Laboratory Department, Clinic “Health House”, Tbilisi, Georgia

³ CEO, OB/Gyn, Reproductologist, Hospital IQ, Tbilisi, Georgia

⁴ Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Background: Human papillomavirus (HPV) is the most common viral cause of cervical cancer worldwide. Persistent infections with high-risk HPV genotypes represent a significant oncogenic risk factor. In Georgia, molecular HPV testing is increasingly being used to investigate abnormal cervical cytology, yet only limited data on genotype distribution are available.

Materials and Methods: A retrospective analysis was performed on 780 cervical smears taken between 2023 and 2025 from women aged 18-55 with abnormal cytology (ASC-US, CIN1, or CIN2). DNA extraction was performed using a kit from Bioron Diagnostics, followed by genotyping using real-time PCR (RealLine HPV HPC Screen Flu format) to detect high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).

Results: HPV DNA from high-risk genotypes was detected in 22% of samples. HPV31, HPV16, HPV52, and HPV51 were the most common, followed by HPV33, HPV56, HPV59, and HPV18. The majority of HPV-positive women had low-grade lesions (CIN1 or ASC-US), while high-grade lesions (HSIL/CIN2) were less common.

Conclusions: The results demonstrate a significant prevalence of high-risk HPV infections in Georgian women with abnormal cervical cytology. The dominance of specific genotypes, especially HPV31 and HPV16, and their prevalence in younger and middle-aged groups, underscores the importance of targeted screening and genotype-specific monitoring to optimize the prevention of cervical cancer.

Keywords: high-risk HPV, cervical cytology, real-time PCR, genotype distribution, Georgia

TETRASOMY X IN AN ADOLESCENT GIRL

ANA JIBLADZE, PhD Student;¹ **JENARO KRISTESASHVILI**, MD, PhD, Prof.;¹

ELENE ASANIDZE, Associate Prof.²

¹ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

² University Geomedi, Tbilisi, Georgia

ABSTRACT

Polysomy X is a group of genetic disorders in which an individual has more than two X chromosomes, such as trisomy X (47,XXX), tetrasomy X (48,XXXX), and pentasomy X (49,XXXXX). These chromosomal variations can lead to developmental, cognitive, and physical symptoms, with severity often correlating with the number of X chromosomes. A significant manifestation in women with polysomy X is premature ovarian insufficiency (POI). Tetrasomy X (48,XXXX) is an extremely rare condition characterized by pronounced variability without specific pathognomonic features, complicating diagnosis and potentially leading to underdiagnosis. About 50% of girls with tetrasomy X have normal pubertal development, while the other 50% experience delayed puberty, partial puberty, or complete puberty with menstrual irregularities and/or POI. POI in patients with tetrasomy X has been described in only a few cases.

We identified the 48,XXXX karyotype in a 17-year-old adolescent girl with tall stature (179 cm), who was referred for evaluation of secondary amenorrhea. Premature ovarian insufficiency was diagnosed based on the results of the examination, which revealed elevated levels of gonadotropins and small ovaries without follicles. The patient had psychomotor retardation (IQ of 59), a speech defect, and minor physical anomalies (micrognathia, high-arched palate, bilateral clinodactyly of the 5th finger on the upper extremities). Mild osteopenia, insulin resistance, and a small, asymptomatic Rathke's cleft cyst in the adenohypophysis were also detected. Karyotype 48,XXXX was identified by G-banding in the culture of peripheral blood lymphocytes.

For the diagnosis of tetrasomy X in patients with premature ovarian insufficiency and psychomotor retardation, karyotyping is advisable despite the scarcity of minor physical anomalies. Timely initiation of estrogen replacement therapy from early puberty in such patients is important, as it ensures completion of pubertal development, controls longitudinal growth, and prevents negative long-term consequences of estrogen deficiency, including osteoporosis. Thus, the description of each new case of tetrasomy X, a rare pathology, is important for better understanding and defining the most characteristic features of its phenotype.

Keywords: 48,xxxx; premature ovarian failure; tall stature; mental retardation; amenorrhea

RARE CASE OF CONCOMITANT PSEUDOHYPOPARATHYROIDISM AND BILATERAL OVARIAN TERATOMA

TEA KHURODZE; VITALI VASHAKIDZE; SOPO JAVELIDZE; BASA GEGESHIDZE; ANA PRUIDZE
David Tvildiani Medical University, Tbilisi, Georgia

ABSTRACT

Background: Pseudohypoparathyroidism (PHP) is a rare inherited disorder characterized by hypocalcemia and hyperphosphatemia due to end-organ resistance to parathyroid hormone. The condition results from mutations in the *GNAS* gene, which encodes the alpha subunit of a G protein. This protein activates adenylate cyclase, regulating hormone production in the thyroid, pituitary, ovaries, and testes. Ovarian teratomas are benign neoplasms that arise from pluripotent germ cells that differentiate into various tissues, including endocrine-related structures. Since *GNAS* mutations impact numerous tissues derived from the mesoderm and ectoderm, there could be a possible developmental link.

Case Presentation: We present a rare case of concomitant pseudohypoparathyroidism and bilateral ovarian teratoma. A 35-year-old Caucasian woman presented with hypocalcemia detected in childhood. A previous diagnosis of subclinical hypothyroidism due to thyroid hypoplasia, with negative anti-thyroid antibodies, had been established, and she was maintained on levothyroxine. At the age of 26, she underwent right ovarian cyst excision (histomorphological study confirmed a teratoma). Eight years later, a dermoid cyst was detected in the left ovary, measuring 30 × 27 × 18 mm, with no growth during regular follow-ups.

She had no other clinically significant medical conditions in her past history, but a family history of ovarian cancer and type 2 diabetes mellitus was noted. Physical examination was unremarkable, except for positive Chvostek and Trousseau signs, as well as shortened 4th metacarpal and 4th metatarsal bones bilaterally. Initial lab tests showed significantly low calcium (4.0 mg/dL), increased PTH (241 pg/mL), phosphorus (5.2 mg/dL), and TSH (5.8 uIU/mL). DEXA scan and other laboratory results were within the reference range. A diagnosis of pseudohypoparathyroidism type 1a was made.

Symptoms improved with combined supplementation of calcitriol, calcium citrate, and 25 mcg levothyroxine. After successful normalization of thyroid function, parathyroid hormone levels, and serum calcium, pregnancy was planned. The patient is currently 22 weeks pregnant.

Conclusion: This is a rare case of concomitant PHP and bilateral ovarian dermoid cysts. While there is no clinical evidence linking the two disorders genetically or pathophysiologically, their co-occurrence in a single patient raises clinical suspicion. This remains an area for further investigation and research.

Keywords: pseudohypoparathyroidism (PHP); ovarian teratomas; hypocalcemia; *GNAS* mutations; pregnancy

THE IMMUNOLOGY OF ENDOMETRIOSIS: HOW IMMUNOLOGICAL KNOWLEDGE IS SHAPING MANAGEMENT STRATEGIES

NINO USTIASHVILI, MD; MARIAM GARIBASHVILI, MD Prof.

Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Endometriosis is a multifactorial disease with a poorly understood pathophysiology. It involves the presence of endometrial-like tissue outside the uterus, leading to dysmenorrhea, chronic pelvic pain, and infertility. Sampson's theory of retrograde menstruation is the most accepted explanation for its origin. However, as this phenomenon occurs in most women but only some develop the disease, other mechanisms must be involved. Growing evidence highlights the importance of the peritoneal immune microenvironment. In affected women, immune surveillance is impaired, allowing ectopic endometrial cells to evade clearance and persist. Various immune cells and cytokines contribute to this dysregulated response. Understanding these factors is essential for developing targeted therapies.

This narrative review synthesizes recent literature exploring the immunopathophysiology of endometriosis, with a focus on the roles of specific immune cells and inflammatory mediators. Studies consistently report dysregulated function of macrophages, dendritic cells, natural killer (NK) cells, and T cells, contributing to a pro-inflammatory milieu and impaired endometrial receptivity. Such immune imbalances not only promote lesion survival but also hinder fertility. Multiple studies demonstrate significant dysregulation of immune cell function in endometriosis, including altered activity of macrophages, dendritic cells, NK cells, and T cells. This immune imbalance contributes to chronic inflammation and impaired endometrial receptivity. Recent clinical research has shown that immunomodulatory therapy, particularly peri-implantation use of TNF- α inhibitors such as adalimumab, may significantly improve implantation and clinical pregnancy rates in IVF cycles with recurrent implantation failure. In an experimental rat model, treatment with rituximab – a monoclonal antibody targeting CD20 on B cells – resulted in a significant reduction in endometriotic implant volumes ($p = 0.001$) and lower immunohistochemical scores ($p = 0.043$), suggesting promising immunosuppressive effects. These findings support the potential of immunomodulatory agents in endometriosis-related infertility. Targeting apoptosis pathways may represent a promising therapeutic avenue. For example, GnRH analogs have been shown to increase pro-apoptotic Bax expression while decreasing

anti-apoptotic Bcl-2, thereby promoting lesion regression. This supports the rationale for immune-based strategies that restore apoptosis-driven clearance of ectopic endometrial cells. While immunomodulation in endometriosis is still an emerging area, it holds significant promise as a future therapeutic strategy grounded in the underlying immunopathophysiology of the disease. Further research is essential to validate its efficacy and define its role in the clinical management of endometriosis.

Keywords: endometriosis; immune therapy; infertility; reproductive immunology

X CHROMOSOME ANOMALIES AS A CAUSE OF NON-IATROGENIC PREMATURE OVARIAN INSUFFICIENCY

JENARO KRISTESASHVILI, MD, PhD, Prof.;¹ **MARIAM CHIPASHVILI**, MD;¹
MAKA JORBENADZE, MD;¹ **ELENE ASANIDZE**, MD;² **NINO SIGUA**, MD³

¹ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

² University Geomedi, Tbilisi, Georgia

³ Laboratory of Clinical Genetics, Tbilisi, Georgia

ABSTRACT

Context: In recent years, the prevalence of **non-iatrogenic premature ovarian insufficiency (POI)** has increased from 1% to 3.6% and has garnered increasing concern. Sex chromosome anomalies are among the leading etiological factors contributing to non-iatrogenic POI.

Objective: To determine the peculiarities of clinical manifestations of POI associated with X chromosome anomalies.

Materials and Methods: A study was conducted on 37 patients with non-iatrogenic POI. All patients underwent clinical, laboratory, and instrumental examinations, including karyotyping with G-banding. Molecular cytogenetic methods were used as needed.

Results: Out of the 37 patients with non-iatrogenic POI, 19 were diagnosed with numerical or structural anomalies of the X chromosome. **Four** patients were diagnosed with Turner syndrome (karyotypes 45,X and 46,X,i(Xq)); **seven** patients demonstrated mosaicism 45,X/46,XX; **three** patients had mosaicism 45,X/47,XXX; **four** had structural anomalies of the X chromosome; and **one** had tetraploidy X. Fourteen of these 19 patients presented with primary amenorrhea and/or delayed sexual development. Three patients with mosaic karyotype 45,X/47,XXX, one patient with tetraploidy X, and one patient with deletion of the long arm of the X chromosome (46,X,del(X)(q24)) experienced spontaneous puberty and later developed secondary amenorrhea. In patients with POI, FSH levels ranged from 28-75 IU/L. In cases of mosaic karyotypes and structural anomalies of the X chromosome, **uterine hypoplasia was observed, and ovaries exhibited a markedly reduced number of follicles.** These patients also showed mild growth retardation and isolated somatic anomalies characteristic of Turner syndrome. In patients with delayed puberty, treatment was initiated with natural estrogens to induce puberty, followed by combined estrogen/progestin hormone therapy until the onset of natural menopause.

Conclusions: For all patients with non-iatrogenic premature ovarian insufficiency, even in the absence of characteristic signs of Turner syndrome, karyotyping is recommended to identify potential chromosomal anomalies. Oocyte donation remains the optimal method to achieve fertility in patients with premature ovarian insufficiency and X chromosome numerical and structural anomalies.

Keywords: premature ovarian insufficiency; x chromosome anomalies; amenorrhea

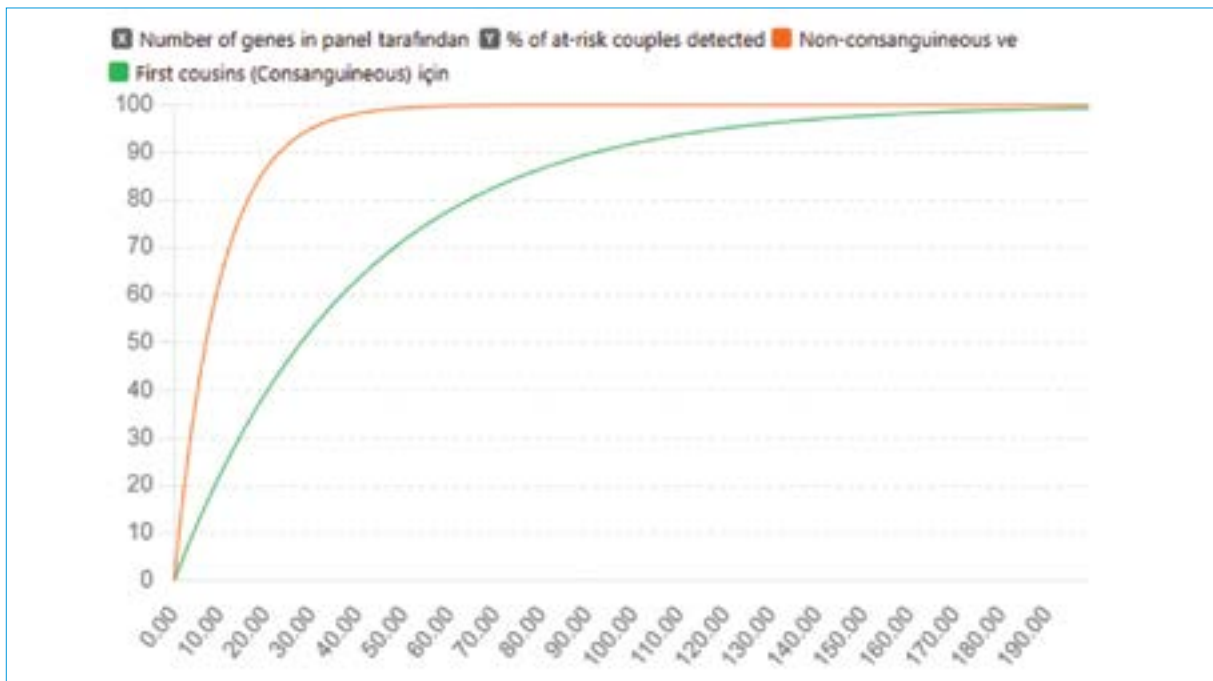
OPTIMIZING DONOR CARRIER SCREENING: STRATEGIES FOR EFFECTIVE MATCHING

EVİRİM ÜNSAL, MD, PhD

*Mikrogen Genetic Diagnosis Laboratory; Department of Clinical Genetics,
Faculty of Medicine, Yüksek İhtisas University, Türkiye*

ABSTRACT

In assisted reproduction, donor selection plays a critical role in minimizing the risk of transmitting autosomal recessive and X-linked disorders. Although comprehensive carrier screening is now routine, effective donor-recipient matching remains challenging because of differences in variant interpretation, interlaboratory variability, and the absence of standardized algorithms. Population-level studies show that ~90% of individuals carry at least one pathogenic variant, with each person harboring an average of two recessive mutations. The probability that a random couple shares the same autosomal recessive disease-causing variant is ~1%, underscoring the importance of robust carrier screening in donor programs.



Fridman et al. (2021) showed that detecting 90% of at-risk couples requires a panel of only 115 genes in non-consanguineous couples, but 749 genes in consanguineous couples, underscoring the value of stratified panel design. Broad exome-based tests increase detection but also add complexity in donor cycles, as positive results require parallel testing of the recipient partner. Therefore, targeted, high-performance panels offer a more practical balance between sensitivity and clinical applicability.

Drawing on 27 years of experience in a population with a high rate of consanguinity, our laboratory has developed **CarrierCheck**, a 146-gene NGS-based panel designed explicitly for donor programs. CarrierCheck overcomes the limitations of standard panels by enabling accurate detection of CNVs, pseudogene-affected genes (e.g., SMN1, CYP21A2, GBA), deep intronic variants, and high-impact genes such as DMD and CFTR – without requiring reflex assays like MLPA. By integrating optimized enrichment, AI-based bioinformatics, and residual risk algorithms, CarrierCheck ensures comprehensive, reliable, and pan-ethnic carrier screening. This approach streamlines donor-recipient matching, reduces reproductive risk, and provides actionable results that align with international best practices.

Keywords: carrier Screening; next-generation sequencing; donor matching; reproductive genetics; consanguinity

EFFECTS OF ORAL DEHYDROEPIANDROSTERONE (DHEA) SUPPLEMENTATION ON HORMONAL PROFILE, MENOPAUSAL CLINICAL SYMPTOMS, AND SEXUAL FUNCTION IN EARLY POSTMENOPAUSAL SYMPTOMATIC CAUCASIAN WOMEN

MARIAMI ANDGULADZE, MD;¹ GEORGE TEVDORASHVILI, MD, PhD²

¹ Medicare, Tbilisi, Georgia

² Tbilisi State Medical University, First University Clinic, Tbilisi, Georgia

ABSTRACT

Background: Dehydroepiandrosterone (DHEA) and its sulfate (DHEAs) are steroid hormones secreted by the adrenal glands. The aging process is associated with declining levels of DHEA and DHEAs, which are thought to contribute to many age-related changes.

Objective: We aimed to evaluate the effects of oral administration of DHEA (50 mg/day) on hormonal profile, menopausal clinical symptoms, and sexual function in early postmenopausal symptomatic Caucasian women at baseline and after 2, 4, and 6 months of treatment.

Methods: In this prospective clinical trial, 42 symptomatic early postmenopausal women (50-55 ± 3.5 years) were selected. Participants were divided into two groups: the study group (n = 22) received oral DHEA 50 mg/day for 6 months, and the control group (n = 20) received placebo.

Serum levels of DHEA, DHEAs, androstenedione (A4), allopregnanolone (3α,5α-THP), progesterone (P4), 17OH progesterone (17OHP), cortisol, testosterone (T), dihydrotestosterone (DHT), estrone (E1), estradiol (E2), SHBG, LH, FSH, and β-endorphin were determined at baseline and after 2, 4, and 6 months. The Menopause Rating Scale (MRS) and the McCoy Female Sexuality Questionnaire (MFSQ) were used before and after treatment.

Results: During treatment, the study group showed a progressive increase in serum levels of DHEA, DHEAs, A4, T, DHT, E2, E1, 3α,5α-THP, and β-endorphin. P4 and 17OHP levels showed only slight increases. By the 4th month, a reduction in cortisol levels was observed. LH and FSH levels gradually decreased, while SHBG levels remained constant.

After 6 months, MRS scores demonstrated progressive improvement of menopausal symptoms, and MFSQ results also improved in the study group.

Conclusions: DHEA administration significantly affected endocrine parameters in early postmenopausal symptomatic Caucasian women and was associated with improvement of menopausal symptoms, sexual function, and psycho-emotional well-being. These findings support

the hypothesis that DHEA administration in symptomatic postmenopausal women helps restore both androgenic and estrogenic balance, thereby reducing most clinical symptoms of the postmenopausal period. On this basis, DHEA may be considered a potentially effective option for menopausal hormone therapy (MHT). However, larger and more specific clinical trials are warranted.

Keywords: dehydroepiandrosterone; DHEAs; menopause; hormone replacement; sexual function; postmenopausal women

WHEN SHOULD HORMONE REPLACEMENT THERAPY BE CONTINUED AFTER THE AGE OF 60 YEARS?

MARTIN BIRKHAUSER, MD

*Professor Emeritus of Gynecological Endocrinology and Reproductive Medicine,
University of Berne, Berne, Switzerland*

ABSTRACT

The median duration of hot flushes considerably exceeds the time frame that is generally accepted in clinical practice. At the age of 65 years, about 25% of all women still suffer from hot flushes. Among a group of women aged 85 years, about 16% experienced hot flushes, and almost 10% were very to moderately distressed by them. Among this group of women aged 85 years, 6.5% were currently needing Menopausal Hormone Therapy (MHT).

Based on the evidence available, there are no reasons to stop MHT in healthy elderly women if climacteric symptoms are not responding to non-hormonal alternatives. In healthy women > 60 years, MHT remains the most effective therapy for vasomotor symptoms and urogenital atrophy. Furthermore, it may alleviate other menopause-related complaints, such as joint and muscle pains, mood swings, sleep disturbances and sexual dysfunction including reduced libido. MHT may also improve quality of life. Continuation of MHT in women > 60 years improves bone quality. Transdermal oestradiol (E2) has no negative effect on the cardio-vascular system. In women beyond the 60s, transdermal E2 combined with micronized progesterone or dydrogesterone (if needed) should be preferred to oral oestrogens. The lowest effective dosage has to be chosen. In some elderly women, half an oestradiol patch of 25 µg twice a week might be sufficient.

Conclusion: The continuation of MHT is indicated in healthy women > 60 years still suffering from severe hot flushes and/or a low quality of life due to oestrogen deficiency. The benefits of transdermal E2 outweigh risks. E2 continues to reduce fracture risk. Decision on continuation has to be based on a woman's individual risk profile. E2 should be given trans-dermally and other progestagens than micronized progesterone or dydrogesterone avoided. There are no reasons to place arbitrary limitations on the duration of MHT.

Keywords: menopausal hormone therapy (MHT); elderly women; vasomotor symptoms; transdermal estradiol (E2); micronized progesterone; quality of life

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„ეუ-ლაბი“-ს პარტნიორი ლაბორატორიები დაკომპლექტებულია ბოლო თაობის ანალიზატორებით. გამოკვლევების სრული ავტომატიზაცია, კომპიუტერული მართვა, ყველა ტექნოლოგიური პროცესისა და გამოკვლევების უნიკალური მეთოდები. ლაბორატორიის პროგრამა მოიცავს ლაბორატორიული მედიცინის ყველა ძირითად სფეროს – რუტინული ანალიზიდან სპეციალიზებულიამდე. ლაბორატორია მუშაობს მედიცინის ყველა სფეროში, ლაბორატორიას შეუძლია შემოგთავაზოთ დაახლოებით 5000 მდე სახეობის გამოკვლევა დიაგნოსტიკის ისეთ დარგებში, როგორიცაა:

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ხარისხის მართვის სისტემა დაფუძნებულია ყველა ლაბორატორიული გამოკვლევების სტანდარტიზაციის პრინციპებზე ინტრალაბორატორიული ხარისხის მართვის ანალიზებზე და ხარისხის გარე შეფასებაზე. ლაბორატორიის მიზანია ხარისხის მართვის სისტემის საშუალებით საიმედო ინსტრუმენტების შექმნა, რათა მინიმუმამდე დავიდეს შეცდომის რისკი. ლაბორატორია ქმნის და აწვდის კლინიკისტს ხარისხიან, ჭეშმარიტ და ობიექტურ ინფორმაციას. DAKKS სერტიფიცირება DIN EN ISO 9001, DIN EN ISO 15189, DIN EN ISO/IEC 17011

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✉ info@eu-lab.ge

HORMONAL CONTRACEPTION: EFFECT ON PEAK BONE MASS

MARTIN BIRKHAUSER, MD

*Professor Emeritus of Gynecological Endocrinology and Reproductive Medicine,
University of Berne, Berne, Switzerland*

ABSTRACT

It is generally accepted that in healthy post-adolescent women and in perimenopausal women, low-dose preparations of combined hormonal contraceptives (CHC) containing 15-20 EE μ g, as well as progestin-only contraceptives, are capable of protecting bone, as do classical COCs delivering 30-35 μ g EE/day. In consequence, it has been believed that low-dose COCs are safe as well and guarantee bone health in users of any age. This assumption has been confirmed in perimenopausal women >40 years of age, where BMD is possibly increased and physiological bone loss prevented.

However, newer evidence shows that this is not the case in younger subgroups of COC users. In adolescents ($\leq$ 18-20 years), the strongly anti-gonadotropic progestins used in COCs containing 15-20 μ g EE may over-suppress the hypothalamic-pituitary-ovarian axis and therefore reduce profoundly endogenous oestrogen production needed for acquiring a normal peak bone mass (PMB). It is worth noting that PMB is not completed until the early twenties. In consequence, a low-dose pill containing 15-20 μ g EE does not guarantee the necessary total oestrogen activity for obtaining a normal PMB as do 30-35 μ g EE COCs.

For the same mechanism, in adolescents, depot-medroxyprogesterone acetate (DMPA) administration may reduce PBM, particularly when given early after menarche. Furthermore, there is strong evidence from longitudinal data that DMPA may significantly affect BMD in adult current users. However, the loss of BMD appears here to be at least partially reversible.

Conclusion: These findings lead to the following recommendations:

1. In adolescents, 30-35 μ g EE COCs are safe for the acquisition of a normal PMB.
2. In contrast, 15-20 μ g EE COCs should not be used in young women until stable ovulatory cycles are reached.
3. DMPA should be avoided in adolescents before PMB is acquired. Initiation of DMPA within the first 3 years after menarche is of particular concern. In adolescents, DMPA should remain a reserve medication where no alternative is possible.

4. For all other methods of hormonal contraception, such as vaginal rings or patches, good evidence is missing in adolescent girls. It is unknown if their use is safe in young women before they reach stable ovulatory cycles and until PBM is completed.

Keywords: hormonal contraception; combined oral contraceptives (COCs); low-dose ethinyl-estradiol (EE); depot-medroxyprogesterone acetate (DMPA); peak bone mass (PBM); bone mineral density (BMD)

CHOICE OF THE PROGESTOGEN FOR MHT IN MENOPAUSAL WOMEN

ALFRED O. MUECK, MD, PharmD, PhD^{1,2}

¹ *University Hospitals of Tuebingen, Department of Women's Health, University Women's Hospital and Research Centre for Women's Health, Tuebingen, Germany*

² *Capital Medical University, Beijing Obstetrics & Gynecology Hospital, and Maternal & Child Health Care Hospital, Department of Gynecological Endocrinology, Beijing, China*

ABSTRACT

With each type of MHT (Menopausal Hormone Therapy), similar good efficacy regarding climacteric symptoms or prevention of osteoporosis and coronary heart disease can be achieved. However, there are differences in terms of possible risks that can be reduced by the choice of type, dosage, and application form of MHT. This should be decided based on the whole evidence, i.e., not only derived from the Women's Health Initiative (WHI) study, where only one type of MHT in one dosage has been tested, equine estrogens with or without combination with MPA (medroxy-progesterone acetate), frequently only used in USA, not in other countries like Europe. There have been many problems in the WHI study, discussed in many publications within the recent 20 years, like in 2/3 of the study population, the start of MHT was too late (mean age 63 years!), 40% had risk factors for cardiovascular diseases and/or breast cancer. It was not a real "placebo-controlled study", because patients and doctors were aware of the medication due to bleeding problems etc. We prefer to treat with the natural estrogen, i.e., estradiol, instead of equine estrogens, which are a mixture of estrogens, components varying to a high degree, and not natural for humans. Likewise, it seems to be reasonable to use the natural progestogen, i.e., progesterone. However, synthetic progestogens are superior to progesterone concerning endometrial efficacy, and the first rule for the choice of a progestogen is to get endometrial protection from developing endometrial cancer. Furthermore, bleeding problems are mostly the first complaints in perimenopause, and often the reason for patients and doctors to withdraw MHT. Although bleeding problems may more often be seen using progesterone compared with synthetic progestogens, it has been demonstrated that using progesterone can also achieve endometrial protection, not only in sequential design (like in the PEPI study, 1996), but also in continuous combined design (like in the REPLENISH study, 2019). Nevertheless, using progesterone, it is advisable to check regularly the endometrium

and bleeding patterns, to use not too low dosages (we recommend 200-300 mg sequentially, 100-200 mg continuously), and to prefer vaginal application if the patient is compliant with this application. Treating in the first official menopause clinic of China about 500 outpatients every day, we have good experience using dydrogesterone, the retro-isomer of progesterone, which has similar positive properties like progesterone, but stronger endometrial efficacy. Using progesterone or dydrogesterone, compared with synthetic progestogens like MPA or NET, NETA, there are less side effects in the metabolic and vascular system (no vasoconstriction) with reduced risk of stroke and venous thromboembolism, and perhaps also less breast cancer risk, as can be suggested from experimental studies and observational trials at least up to 5-8 years. However, more studies are needed for confirmation. The beneficial cardiovascular effects of estrogens are not antagonized, with advantages, e.g., for patients with (risk of) diabetes or metabolic syndrome. Thus, our choice of MHT is mostly estradiol, often as a transdermal application, combined with progesterone orally or preferably vaginally, and in patients with bleeding patterns, combined with oral dydrogesterone

Keywords: menopausal hormone therapy (MHT); progestogens; progesterone; dydrogesterone; breast cancer risk; cardiovascular effects

BREAST CANCER CAUSED BY MHT: THE TWO MAIN MECHANISMS [AND HOW TO REDUCE THE RISK]

ALFRED O. MUECK, MD, PharmD, PhD;^{1,2} **XIANGYAN RUAN**, MD, PhD^{1,2}

¹ University Hospitals of Tuebingen, Department of Women's Health, University Women's Hospital and Research Centre for Women's Health, Tuebingen, Germany

² Capital Medical University, Beijing Obstetrics & Gynecology Hospital and Maternal & Child Health Care Hospital, Department of Gynecological Endocrinology, Beijing, China

ABSTRACT

For the development of breast cancer during MHT (Menopausal Hormone Therapy), according to WHO, two main mechanisms are known: (1) Proliferation mechanisms, induced primarily by estrogens, but possibly strongly enhanced by progestogens, and (2) Development of potential genotoxic (carcinogenic) estrogen metabolites, which may be further increased by certain progestogens. In the past 20 years, we have researched both mechanisms, in collaboration between the University of Tuebingen (Germany) and Capital Medical University, Beijing (China), especially with respect to mechanism (1). We were encouraged by editorials on our first studies, suggesting that the results in WHI could be explained by the overexpression of PGRMC1 in a larger part of the study population, a multifunctional receptor belonging to the MAPR family (Menopause 2011;18:833-834; 2013; 20:486-487). We started with in-vitro experiments in different breast cancer (BC) cells (e.g. *Menopause* 2005;12:468-474; 2011;18:845-850; 2013;20:504-510; *Maturitas* 2013;76:129-133; *Climacteric* 2012;15:467-472; 2013;16:509-513; *Gynecol Endocr* 2012;28:863-866; 2013;29:160-163), we continued with different animal studies (*Maturitas* 2017;102:26-33; 2019;123:1-8; *Gynecol Endocr* 2020;36:1024-1027), and finally we performed clinical studies with breast cancer patients (*Menopause* 2017;24:203-209; 2020;27:183-193; *Maturitas* 2020;140:64-71). In-vitro studies showed dose- and time-dependent BC-cell proliferations in the presence of PGRMC1 with all available synthetic progestogens but not with progesterone. Likewise, synthetic progestogens but not progesterone increased the E2-induced PGRMC1-tumor-proliferation in animals. In our clinical studies, PGRMC1 in BC-tissue could be correlated to tumor characteristics like tumor diameter, grade, metastatic status, disease-free, and overall survival. After developing an assay, we could correlate blood levels of PCRMC1 with BC-tissue, demonstrating PGRMC1 to be superior to tumor markers such as CEA, CA125, CA153. So PGRMC1 could be used as a

new tumor marker to predict breast cancer risk before the use of MHT. Regarding mechanism (2), besides the central metabolism of estradiol (E2) in the E-steroid-ring via estrone to estrinol in less amount in the A-steroid-ring, catechol-estrogens (2- and 4-OH-E2) are produced, which can be further metabolized to carcinogenic quinones, if protective enzyme systems are disturbed, e.g., by genetic polymorphisms. Assessing multiple polymorphisms could be a key factor in reducing the risk before starting MHT. Furthermore, within two case-control studies (*Ruan et al., Arch Gynecol Obstet 2015;291:1141-1146*), we demonstrated that the ratio of 2/16-OH-E2 can be used for predicting BC risk, a finding confirmed by other groups. Our ongoing research is investigating whether the carcinogenic quinones themselves could be assessed. They, together with intermediate semiquinones, react to stable complexes, which can be assessed with fluorescence spectroscopy (Ruan, Mueck, *Climacteric 2023; 26: 263-270*). However, the absolute prerequisite for this is unrestricted oxidative cell stress, so mechanism(2) may be only important, e.g., together with smoke or in areas of industrial pollution.

Keywords: menopausal hormone therapy (MHT); breast cancer; PGRMC1; synthetic progestogens; estrogen metabolites; breast cancer risk prediction

FEATURES OF HORMONAL CHANGES IN WOMEN OF REPRODUCTIVE AGE WITH HYPERANDROGENISM SYNDROME

NATAVAN AKHUNDOVA, MD, PhD, Prof.

Department of Obstetrics and Gynecology, Azerbaijan Medical University, Baku, Azerbaijan

ABSTRACT

Background: One of the most critical problems in endocrinological gynecology is hyperandrogenism (HA) syndrome. Despite the abundance of research, scientific data on pathogenesis, clinical and diagnostic features, and modern methods of correction remain limited and contradictory. Changes in the hypothalamic-pituitary-ovarian-adrenal system in women with HA lead to menstrual and reproductive dysfunction, excessive hair growth in androgen-dependent areas of the skin, changes in appearance, voice, skin, musculoskeletal system, mammary glands, and genitalia. These changes have a profound impact on a woman's psychological state. Hyperandrogenism syndrome in reproductive-aged women occurs as a result of pathologies in the central regulatory mechanisms of ovarian and adrenal activity.

Objective: To study hormonal changes in women of reproductive age with hyperandrogenism syndrome.

Materials and Methods: The study included 367 women of reproductive age with HA syndrome and a control group of 20 healthy women. The mean age of patients was 28.57 ± 0.45 years (range, 19-44 years). All women with HA syndrome underwent hormonal testing before and after pathogenetic treatment, with comparisons made to the control group.

Serum levels of the following hormones were determined: follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH ratio, thyroid-stimulating hormone (TSH), prolactin (Prl), estradiol (E2), estrone (E1), total testosterone (Ttotal), dehydroepiandrosterone sulfate (DHEA-S), androstenedione (An), cortisol (C), 17-hydroxyprogesterone (17-OHP), free triiodothyronine (T3-free), free thyroxine (T4-free), sex hormone-binding globulin (SHBG), and anti-Müllerian hormone (AMH).

Hormones were determined: a) in fully automatic mode; b) using Abbott Architect reagents; c) by electrochemiluminescence (ECL); d) with the Architect i1000 analyzer (Abbott, USA). AMH was determined using chemiluminescence on the Cobas e 411 system (Switzerland). 17-OHP, An, and E1 were determined manually by enzyme-linked immunoassay (ELISA) with Human (Germany) reagents. SHBG was measured by electrochemiluminescence on the Cobas e 411 analyzer.

Results and Discussion: Among the causes of hyperandrogenism in reproductive-aged women, polycystic ovary syndrome (PCOS) (32.7%), hyperprolactinemia (18.5%), and hypothyroidism (12.5%) were the most common. Less frequent causes include obesity (6.3%), hyperthyroidism (4.6%), hypogonadotropic hypogonadism (6.8%), hypergonadotropic hypogonadism (5.7%), drug-induced hyperandrogenism (2.5%), adrenal pathologies (3.5%), and ovarian or adrenal tumors (1.9%).

Women with HA syndrome showed elevated levels of LH (11.57 ± 0.53 mIU/mL), LH/FSH ratio (1.9 ± 0.09), E1 (124.16 ± 3.42 ng/mL), 17-OHP (1.0 ± 0.04 ng/mL), Ttotal (1.0 ± 0.04 ng/mL), C (124.82 ± 1.75 ng/mL), An (3.27 ± 0.07 ng/mL), DHEA-S (2.96 ± 0.13 pg/mL), and reduced levels of E2 (70.97 ± 2.1 pg/mL) and SHBG (43.46 ± 1.53 nmol/L).

After pathogenetic treatment, significant decreases were observed in LH (8.36 ± 0.25 mIU/mL), LH/FSH ratio (1.39 ± 0.08), Prl (11.21 ± 0.26 ng/mL), TSH (1.91 ± 0.05 μ IU/mL), E1 (90.13 ± 1.24 ng/mL), 17-OHP (0.66 ± 0.01 ng/mL), Ttotal (0.64 ± 0.01 ng/mL), An (2.49 ± 0.03 ng/mL), and DHEA-S (1.99 ± 0.06 pg/mL), while levels of E2 (79.91 ± 1.0 pg/mL), T3-free (2.32 ± 0.04 pg/mL), T4-free (1.18 ± 0.01 ng/dL), and SHBG (61.0 ± 0.92 nmol/L) significantly increased ($P < .05$).

Keywords: hyperandrogenism; reproductive age; hormonal changes; polycystic ovary syndrome; reproductive endocrinology

DIAGNOSIS AND MANAGEMENT OF PREGNANCY IN A PATIENT WITH NONCLASSIC CONGENITAL ADRENAL HYPERPLASIA (NCCAH) AND RECURRENT PREGNANCY LOSS (RPL)

SOPHIO KVALIASHVILI, MD, PhD;^{1,2,3} JENARO KRISTESASHVILI, MD, PhD;^{4,5}

MARIAM CHIPASHVILI, MD, PhD;^{2,4} MAKAR JORBENADZE, MD;^{2,4} NINO KURASHVILI, MD²

¹ Pineo Medical Ecosystem, Tbilisi, Georgia

² Zhordania Medical Center, Tbilisi, Georgia

³ Cito Medical Center, Tbilisi, Georgia

⁴ Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

⁵ Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Nonclassic congenital adrenal hyperplasia (NCCAH) is a mild and often underdiagnosed form of congenital adrenal hyperplasia caused by partial 21-hydroxylase deficiency. It is characterized by androgen excess and may present with symptoms such as hirsutism, oligomenorrhea, and subfertility. Women with NCCAH are at an increased risk for recurrent pregnancy loss (RPL), yet diagnosis is frequently delayed due to mild or nonspecific clinical features.

Objective: To present a case of successful pregnancy management in a patient with previously undiagnosed NCCAH and a history of recurrent pregnancy loss.

Materials and Methods: A 29-year-old woman with three consecutive first-trimester miscarriages underwent a comprehensive evaluation for RPL, including genetic, anatomical, autoimmune, thrombophilic, and hormonal workup. Elevated serum 17-hydroxyprogesterone, testosterone, and androstenedione levels raised suspicion of NCCAH. An ACTH stimulation test was inconclusive, prompting genetic testing, which confirmed compound heterozygous mutations (Q318X and P453S) in the CYP21A2 gene. The patient received preconception dexamethasone therapy and was switched to methylprednisolone upon pregnancy confirmation.

Results: Following glucocorticoid therapy, the patient achieved a successful pregnancy. Steroid treatment was discontinued at 11 weeks after noninvasive prenatal testing confirmed a male fetus. She delivered a healthy male infant with normal genitalia and karyotype. At three years of age, the child exhibited normal growth and development.

Conclusions: This case underscores the importance of considering NCCAH in women with unexplained infertility or RPL. Biochemical and genetic testing are essential for accurate diagnosis,

particularly when stimulation tests are inconclusive. Glucocorticoid therapy can restore fertility and reduce miscarriage risk, while genetic counseling supports informed reproductive decision-making. Early recognition and management of NCCAH can lead to favorable maternal and fetal outcomes.

Keywords: nonclassic congenital adrenal hyperplasia; miscarriage; pregnancy; glucocorticoids; dexamethasone

EARLY DIAGNOSIS OF RISK FACTORS FOR PREECLAMPSIA DURING THE INITIAL STAGE OF PREGNANCY

LALI GOGIA, MD

Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Preeclampsia is one of the most severe complications during pregnancy, posing significant risks to both maternal and fetal health.

Objective: To evaluate the benefits of early diagnosis of preeclampsia risk factors and the effectiveness of the ASTRAIA screening program.

Materials and Methods: The ASTRAIA screening model was used, which integrates ultrasound imaging, biochemical analyses, and individual clinical data during weeks 11-13 of pregnancy.

Results: Findings indicate that ASTRAIA significantly improves diagnostic accuracy and supports the planning of preventive interventions.

Conclusions: Technological integration in screening plays a vital role in forecasting preeclampsia and ensuring a safer pregnancy.

Keywords: preeclampsia; ASTRAIA; early diagnosis; biomarkers; pregnancy complications

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პრეკლამფიის განვითარების რისკ-ფაქტორების ადრეული დიაგნოსტიკა ორსულობის საწყის ეტაპზე

ლალი ბობია, MD

ქართულ გერმანული რეპროდუქციის ცენტრი, თბილისი, საქართველო

აბსტრაქტი

შესავალი: პრეკლამფია წარმოადგენს ერთ-ერთ ყველაზე რთულ გართულებას ორსულობის პერიოდში, რომელიც საფრთხეს უქმნის დედისა და ნაყოფის ჯანმრთელობას.

მიზანი: შეფასდეს პრეკლამფიის რისკ-ფაქტორების ადრეული დიაგნოსტიკის საგებლი და ASTRAIA-ს სკრინინგული პროგრამის ეფექტურობა.

მასალა და მეთოდები: გამოყენებულ იქნა ASTRAIA-ს სკრინინგული მოდელი, რომელიც აერთიანებს ულტრაბგერით კვლევას, ბიოქიმიურ ანალიზებს და ინდივიდუალურ მონაცემებს ორსულობის 11-13 კვირაში.

შედეგები: მიღებული შედეგები მიუთითებს, რომ ASTRAIA-ს გამოყენება მნიშვნელოვნად ზრდის დიაგნოსტიკის სიზუსტეს და ხელს უწყობს პრევენციული ნაბიჯების დაგეგმვას.

დასკვნა: ტექნოლოგიური ინტეგრაცია სკრინინგში წარმოადგენს მნიშვნელოვან ნაბიჯს პრეკლამფიის პროგნოზირებისთვის და უსაფრთხო ორსულობის უზრუნველყოფისთვის.

საძიებო სიტყვები: პრეკლამფია, ASTRAIA, ადრეული დიაგნოსტიკა, ბიომარკერები, ორსულობის გართულებები

THE IMPACT OF MATERNAL OBESITY ON PREGNANCY OUTCOMES: A CROSS-SECTIONAL COHORT STUDY

VAKHTANG GURABANIDZE, MD, Doctorate; **TINAT GAGUA**, MD, PhD, Prof.

Obstetrician-Gynecologist, Gagua Clinic, Davit Tvildiani Medical University, Tbilisi, Georgia

ABSTRACT

Background: Maternal obesity is a growing global health concern with significant implications for maternal and fetal health.

Objective: To investigate the association between maternal body mass index (BMI) and key pregnancy outcomes in a clinical cohort. (changed from *This study investigated* → more standard objective phrasing)

Materials and Methods: A cross-sectional cohort study was conducted in the OB/GYN Department of Gagua Clinic, Davit Tvildiani Medical University (corrected from *Gaguac Clinic, David Tvildiani*). From January 2023 to January 2025, 300 pregnant women were enrolled and categorized into three groups:

- Normal weight (BMI 18.0-25.0 kg/m²; n=94)
- Overweight (BMI 25.1-29.9 kg/m²; n=124)
- Obese (BMI ≥30.0 kg/m²; n=82)

Outcomes included gestational age at delivery, mode of delivery, and neonatal birth weight percentiles. Statistical analysis was performed using the chi-square test, with $p < 0.05$ considered significant.

Results:

- Mean gestational age at delivery: 39.0 ± 1.4 weeks (normal weight), 39.0 ± 1.2 weeks (overweight), 39.4 ± 1.1 weeks (obese) ($p=0.09$).
- Preterm birth rates: 6.4% (normal weight), 7.3% (overweight), 13.7% (obese) ($p=0.21$).
- Cesarean section rates: 53.7% (normal weight), 62.8% (overweight), 68.1% (obese) ($p=0.03$).
- Newborns with birth weight in lowest or highest percentiles: 0.0% (normal weight), 14.5% (overweight), 41.5% (obese) ($p < 0.001$).

Conclusions: Maternal obesity is significantly associated with increased rates of cesarean section and abnormal fetal growth. Early BMI assessment, targeted antenatal interventions, and close monitoring throughout pregnancy are essential to reduce obesity-related obstetric complications.

Keywords: pregnancy complications; maternal obesity; fetal growth restriction; cesarean section (changed from *C-section* → standardized scientific terminology)

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THE EFFICACY OF PESSARY IN PRETERM BIRTH PREVENTION IN MULTIFETAL PREGNANCIES

REVAZ SULUKHIA, MD, Prof.;¹ LARISA MELIA; ALEKSANDER SULUKHIA; NINO DAVIDOVA

¹ Faculty of Medicine, European University, Tbilisi, Georgia

ABSTRACT

Background: Premature birth, both spontaneous and iatrogenic, represents a serious problem in modern obstetrics. Preterm birth (PTB) is one of the most significant causes of perinatal morbidity and mortality and is the leading cause of death in children under 5 years of age worldwide. The frequency of spontaneous preterm birth accounts for 65-70% of all preterm births, while the iatrogenic preterm birth rate amounts to 30-35%. We studied the influence of various factors on the development of premature birth.

Aim of the study: To assess the efficacy of pessary use in preterm birth (PB) prevention in patients with multifetal pregnancies.

Materials and Methods: A retrospective cohort study was conducted in the Perinatal Department of Gudushauri National Medical Center from 2020 to 2024 and included 226 women with multifetal pregnancies and threatened PB. The patients were divided into three groups: group I – 68 patients who conceived naturally and in whom a pessary was used to prevent preterm delivery; group II – 84 pregnant women after assisted reproductive technologies (ART) with pessary treatment for PB prevention; and group III – 74 women with threatened preterm delivery in whom a pessary was not used. In all cases, the pessaries were inserted between 14-24 weeks of gestation.

Results: In group I, the frequency of late preterm delivery ($n = 35$, 51.47%) was statistically significantly higher compared with moderate ($n = 24$, 35.29%), very preterm ($n = 7$, 10.29%), and extremely preterm ($n = 2$, 2.94%) delivery rates ($p = .000$). The same tendency was revealed in patients after IVF with pessary insertion, as well as in patients without pessary use ($p = .000$). However, a statistically significant difference was not found when comparing rates between groups ($p > .05$).

Conclusion: The use of a pessary in multifetal pregnancies should be regarded as supportive therapy, as it may prolong pregnancy; however, it does not prevent preterm delivery.

Keywords: preterm birth; cervix insufficiency; twin gestation

SPONTANEOUS HETEROTOPIC PREGNANCY: A RARE DIAGNOSTIC CHALLENGE IN EARLY GESTATION – A CASE PRESENTATION

LANA EZIESHVILI, MD;¹ NATIA PKHALADZE, MD;² SOPHIA TAMAZASHVILI, MD³

¹ Department of Radiology, TSMU First University Clinic, Tbilisi, Georgia

² Department of Obstetrics and Gynecology, TSMU First University Clinic, Tbilisi, Georgia

³ Department of Obstetrics and Gynecology, David Davarashvili Clinic, Tbilisi, Georgia

ABSTRACT

Background: Heterotopic pregnancy (HP) refers to the simultaneous occurrence of intrauterine and ectopic gestations. While more frequently observed following assisted reproductive technologies (ART), spontaneous cases remain exceedingly rare, with an estimated incidence of 1 in 30,000 pregnancies. Early diagnosis is essential to prevent tubal rupture and maternal morbidity.

Case Presentation: A 30-year-old gravida 2, para 1 (G2P1) woman with no history of ART or identifiable risk factors presented at 6 weeks of gestation with lower abdominal pain and spotting. Transvaginal ultrasound revealed a viable intrauterine pregnancy alongside a right tubal ectopic pregnancy and free fluid in the pouch of Douglas, raising suspicion of rupture.

Management and Outcome: The patient underwent emergency laparoscopic right salpingectomy. The intrauterine pregnancy was preserved, and she later delivered a healthy term neonate.

Discussion: This case highlights the diagnostic complexity of HP, which can be overlooked due to the reassuring presence of an intrauterine pregnancy. Transvaginal ultrasound remains the cornerstone of diagnosis, and timely surgical intervention is critical, especially when rupture is suspected.

Conclusion: Clinicians should maintain a high index of suspicion for heterotopic pregnancy, even in spontaneous conceptions without risk factors. Prompt recognition and intervention can preserve both maternal health and intrauterine gestation.

Keywords: ectopic pregnancy; intrauterine pregnancy; transvaginal ultrasound; pregnancy complications; gynecologic emergencies

CERVICAL CANCER IN PREGNANCY

DINA KURDIANI, PhD, MD;¹ NINO SHARIKADZE, MD;² IRAKLI ZHVANIA, MD³

¹ *Institute of Clinical Oncology, Tbilisi, Georgia*

² *Oncology Department, Mardaleishvili Medical Centre, Tbilisi, Georgia*

³ *Institute of Clinical Oncology, Tbilisi, Georgia*

ABSTRACT

Background: Cervical cancer is the fourth most common cancer worldwide. In Georgia, it is the fifth most common malignancy, typically diagnosed in the fifth decade of life. According to the National Center of Disease Control and Public Health (NCDC), 322 new cases of cervical cancer were reported in 2019, accounting for 5.6% of all cancers diagnosed that year. A decreasing trend was noted in 2016-2018; however, incidence rose again in 2019, to 5.6 per 100,000. The mortality rate is also increasing, reaching 8.5 per 100,000 in 2019. The overall prognosis in Georgia is poor, with a 5-year survival rate of 56.9%.

Between 1% and 3% of women with cervical cancer are pregnant or postpartum at diagnosis [1,2]. Approximately half of these cases are diagnosed prenatally, while the other half are identified within 12 months after delivery [3]. Cervical cancer is one of the most common malignancies in pregnancy, with an estimated incidence of 0.8-1.5 cases per 10,000 births.

Materials and Methods: Large randomized trials are lacking to guide the management of pregnant patients with cervical cancer. Therefore, recommendations are based on evidence from trials in nonpregnant women, observational studies of pregnant women, and the unique medical and ethical considerations of each case. Treatment should be individualized according to cancer stage, maternal wishes regarding pregnancy continuation, and the risks of delaying or modifying therapy during gestation.

Results:

- Every woman diagnosed with cervical cancer must be counseled by a multidisciplinary team including a gynecologic oncologist and obstetrician.
- The treatment plan should be based on tumor stage and gestational age at diagnosis.
- Preferred imaging is MRI or ultrasound.
- Treatment options depend on tumor stage and gestational week; risks and benefits should be carefully discussed with the patient.

- For stage IA and IB tumors <2 cm with negative lymph nodes, conization or simple cervical resection is recommended. Delay of treatment until the second trimester (to allow fetal lung maturity) may be acceptable.

Before 24 weeks:

- In lymph node-positive stage IB1 tumors <2 cm, pregnancy termination is advised. If the patient wishes to continue pregnancy, neoadjuvant chemotherapy (NACT) from the second trimester onward, followed by postpartum chemoradiotherapy, is possible.
- In stage IB1 tumors >2 cm, NACT is recommended regardless of nodal status.
- Preferred NACT regimen: cisplatin 50-100 mg/m² every 3 weeks.
- Carboplatin/paclitaxel may also be considered.

After 25 weeks:

- NACT can stabilize the disease while awaiting fetal lung maturity.
- NACT is not recommended after 33 weeks due to the high risk of preterm birth.
- Delivery should be by cesarean section.

Conclusions: Management of cervical cancer in pregnancy requires careful balancing of maternal prognosis and fetal outcomes. Individualized treatment by a multidisciplinary team, with stage-specific and gestational-age-appropriate strategies, is essential for optimal care.

Keywords: cervical cancer; pregnancy; neoadjuvant chemotherapy; conization; cesarean section

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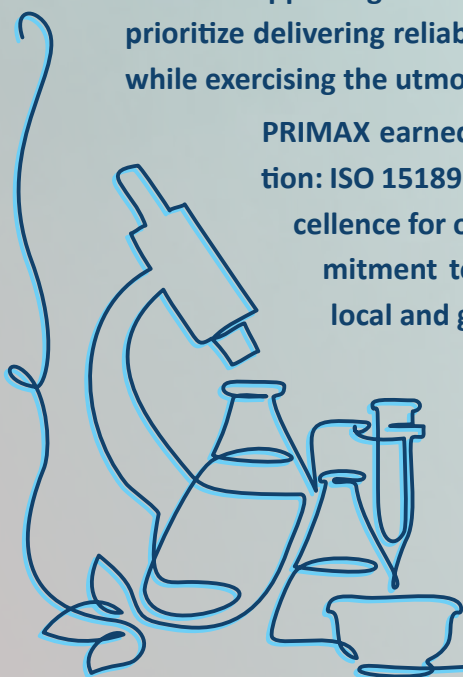
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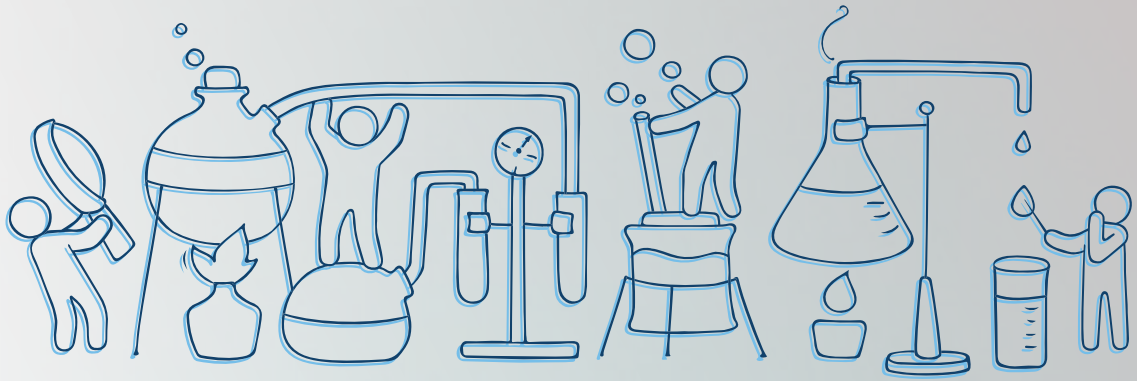
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მოლეკულური მედიცინის კვლევითი ცენტრი - პრაიმაქსი წარმოადგენს სამედიცინო დაწესებულებას, რომელიც გთავაზობთ მაღალი ხარისხის თანამედროვე დიაგნოსტიკურ კვლევებს, გამდინარე ციტომეტრიისა და მოლეკულურ-გენეტიკური ტესტირების მეთოდებით.

ჩვენი ცენტრი აღჭურვილია მოწინავე ტექნოლოგიებით და დაკომპლექტებულია მაღალკვალიფიციური პერსონალით, რაც უზრუნველყოფს მაღალი სანდოობის კვლევების შესრულებას და პაციენტზე მორგებულ პერსონალიზებული სამედიცინო რეკომენდაციების გაცემას.

ჩვენს კვლევით ცენტრში წარმოდგენილია მულტიდისციპლინური დიაგნოსტიკური მიმართულებები, მათ შორის, პემატოლოგია, ციტოლოგია, გამდინარე ციტომეტრია, კლინიკური ბიოქიმია, მოლეკულური მიკრობიოლოგია და მოლეკულურ-გენეტიკური დიაგნოსტიკა.

ცენტრის ლაბორატორიებში სხვადასხვა მოლეკულურ-გენეტიკური ტექნიკის გამოყენებით, საშუალება გვაქვს, მივიღოთ დეტალური ინფორმაცია დაავადების გენეტიკურ საფუძვლებზე, დავადგინოთ სხვადასხვა პათოლოგიებთან ასოცირებული პათოგენური მუტაციები და გენური აბერაციები. ცენტრში წარმოდგენილი სერვისების კრიტიკული მნიშვნელობიდან გამომდინარე, ჩვენი გუნდი ზედმიწევნით პასუხობს უმაღლეს სტანდარტებს და უზრუნველყოფს კვლევების ხარისხის კონტროლისა და პაციენტის პერსონალური სამედიცინო მონაცემების მკაცრად დაცვას. აღნიშნული პრინციპების გატარება აისახება საიმედო შედეგებში, რაც პაციენტისთვის პერსონალიზებული და ოპტიმალური მკურნალობის შერჩევის მნიშვნელოვან წინაპირობას წარმოადგენს.

პრაიმაქსმა წარმატებით გაიარა AB Certification-ის საერთაშორისო აკრედიტაცია და მიენიჭა ISO 15189:2022 და ISO 9001:2015 სერტიფიკატები, რომლებიც ადასტურებს სამედიცინო ლაბორატორიისა და ორგანიზაციის მენეჯმენტის საერთაშორისოდ აღიარებულ ხარისხს. ეს მიუთითებს კომპანიის მზაობაზე, დააკმაყოფილოს როგორც ადგილობრივი, ისე საერთაშორისო ბაზრის მოთხოვნები და პაციენტებს შესთავაზოს უმაღლესი სტანდარტის სამედიცინო მომსახურება.

პრაიმაქსის მიზანია მოწინავე დიაგნოსტიკური ტექნოლოგიების, მოლეკულური გენეტიკის მიღწევებისა და ზუსტი კვლევების გამოყენებით მნიშვნელოვნად გაიზარდოს ჯანდაცვის ეფექტურობა, განვითარდეს და დაიხვეწოს პერსონალიზებული, პაციენტზე ორიენტირებული მედიცინა საქართველოში.

PREGNANCY COMPLICATIONS IN CONGENITAL HYPOFIBRINOGENEMIA ASSOCIATED WITH MTHFR (C677T) GENOTYPE: A REPORT OF TWO CASES

MAIA JANELIDZE, MD, PhD;¹ TAMAR MATITASHVILI, MD;²

SHORENA TCHIOKADZE, MD, PhD²

¹ IQ Clinic, Tbilisi, Georgia

² Health House, Tbilisi, Georgia

ABSTRACT

Background: Congenital hypofibrinogenemia, defined as plasma fibrinogen levels below 150 mg/dL, is a rare hereditary bleeding disorder. Owing to its rarity and limited reports in the literature, there is a significant knowledge gap regarding pregnancy complications and the management of this high-risk disease. Due to a deficiency or defect of the fibrinogen molecule, congenital hypofibrinogenemia is associated with severe obstetric complications. Paradoxically, this condition may also predispose to thrombotic events.

Case Description: We present two cases of this hereditary disease leading to severe pregnancy-related complications.

- Case 1: A 28-year-old woman diagnosed with hypofibrinogenemia and homozygous for the MTHFR C677T genotype. Her fibrinogen level reached a nadir of 80 mg/dL. After an uncomplicated delivery at 41 weeks, she developed bilateral pulmonary embolism (PE) and inferior vena cava (IVC) thrombosis three weeks postpartum, requiring placement of an IVC filter.
- Case 2: A 34-year-old patient experienced intrauterine fetal demise at 30 weeks. Her lowest fibrinogen level was 61 mg/dL. Genetic testing confirmed a homozygous MTHFR C677T mutation.

Discussion: Unlike the favorable outcomes reported in the most significant published cohort to date, both of our patients experienced serious obstetric and postpartum complications. Importantly, both women carried an additional risk factor – homozygous MTHFR C677T genotype – potentially compounding the thrombotic risk.

Conclusion: Women with congenital hypofibrinogenemia require comprehensive thrombophilia screening and careful multidisciplinary counseling regarding the risks of severe maternal and fetal complications during pregnancy and postpartum. In select cases, the option of a gestational carrier should be discussed.

Keywords: congenital hypofibrinogenemia; pregnancy complications; MTHFR C677T; thrombophilia; pulmonary embolism.

THE IMPACT OF POST-CESAREAN SECTION ISTHMOCELE ON REPRODUCTIVE HEALTH

ANA GHVINIASHVILI, MD, PhD Candidate;^{1,2} MARIAM KHARAISHVILI, MD, PhD³

¹ New Vision University, Tbilisi, Georgia

² Professor Zhordania and Professor Khomasuridze Institute of Reproductology, Tbilisi, Georgia

³ Georgian American University (GAU), Tbilisi, Georgia

ABSTRACT

Background: An isthmocele, also known as a cesarean scar defect, is a uterine niche resulting from inadequate healing of the myometrial incision after cesarean section. With the global rise in cesarean section rates, the prevalence of isthmocele has increased significantly, and is currently estimated between 19% and 70%. It is now recognized as a distinct clinical entity associated with various gynecological and reproductive complications.

Objective: To assess the impact of isthmocele on reproductive health, identify associated risk factors, and evaluate the frequency and nature of complications.

Materials and Methods: A retrospective analysis and follow-up survey were conducted on 250 women with prior cesarean sections (2021-2025). Participants were divided into two groups: Group I – patients with isthmocele (n = 82), and Group II – a control group without isthmocele (n = 168). Data were collected through medical records and structured surveys. Statistical analysis was performed using SPSS 23.0 software, and odds ratios (OR) with 95% confidence intervals were calculated. A p-value < 0.05 was considered statistically significant.

Results: Isthmocele was identified in 32.8% of cases. Its occurrence was significantly higher among women aged ≥30 years (71.9% vs 54.2%; OR = 2.17, p < 0.001) and those with two or more prior cesarean deliveries (34.1% vs 22.0%; OR = 1.83, p = 0.046). A history of induced abortion was more prevalent in the isthmocele group (24.4% vs 11.9%; OR = 2.39, p = 0.013), as was spontaneous abortion (35.4% vs 14.9%; OR = 3.13, p < 0.001). Patients with isthmocele were more likely to report menstrual cycle disorders (45.1% vs 32.1%; OR = 1.74, p = 0.046), abnormal uterine bleeding (39.0% vs 21.4%; OR = 2.34, p = 0.004), and chronic pelvic pain (35.4% vs 19.6%; OR = 2.24, p = 0.008). Notably, secondary infertility was diagnosed in 9.8% of women with isthmocele compared to 1.2% in the control group (OR = 8.97, p = 0.006).

Conclusions: Isthmocele development is significantly associated with advanced maternal age, multiple cesarean deliveries, and abortion history. This defect correlates with a higher incidence of menstrual abnormalities, chronic pelvic pain, and secondary infertility, underscoring its detrimental impact on reproductive health. Findings emphasize the importance of clinical vigilance, standardized diagnostic criteria, and timely management.

Keywords: isthmocele; uterine niche; cesarean section; reproductive health; infertility

DIAGNOSTIC CAPABILITIES FOR MÜLLERIAN ANOMALIES IN WOMEN WITH REPRODUCTIVE DISORDERS

IA CHAPIDZE, MD, PhD student;^{1,2,3} **JENARO KRISTESASHVILI**, MD, PhD, Prof.^{1,2}

¹ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

² Center for Reproductive Medicine “Universe”, Tbilisi, Georgia

³ Clinic “Invitro Life”, Tbilisi, Georgia

ABSTRACT

Background: Müllerian duct anomalies (MA) are a heterogeneous group of congenital anomalies. Early detection and accurate diagnosis are essential to distinguish operable from inoperable cases. MA are recognized causes of primary infertility (PI) and recurrent pregnancy loss (RPL). In recent years, advances in diagnostic methods and their clinical implementation have significantly improved the detection of MA.

Objective: To determine the frequency and types of MA in women with reproductive disorders and to evaluate the diagnostic capabilities of three-dimensional (3D) transvaginal ultrasonography.

Materials and Methods: A prospective, comparative, case-control study was conducted on 3,973 women aged 16-45 years who visited the Center for Reproductive Medicine “Universe” between 2019 and 2023. Among them, 2,394 had primary infertility (Group I), 898 had RPL (Group II), 61 had primary amenorrhea (Group III), and 620 women with one or more full-term live births served as the control group (Group IV). All underwent two-dimensional and 3D transvaginal ultrasonography. Additional evaluations included hysterosalpingography (49 women), hystero-laparoscopy (53 women), and magnetic resonance imaging (30 women).

Results: The most common MA identified in Groups I and II was a septate uterus. For its diagnosis, 3D ultrasonography demonstrated a sensitivity of 95.83% and specificity of 100% compared with MRI, with a κ index of 0.978. Compared with hystero-laparoscopy, 3D ultrasonography demonstrated a sensitivity of 97.5% and specificity of 100% ($\kappa = 0.987$). Compared with hysterosalpingography, MRI, and hystero-laparoscopy, 3D ultrasonography demonstrated 100% sensitivity and specificity for all other anomalies.

Conclusion: Three-dimensional ultrasonography is a rapid, cost-effective, noninvasive, and highly informative method for evaluating MA. It demonstrated excellent concordance with MRI, confirming its role as a primary diagnostic tool in reproductive medicine.

Keywords: müllerian anomalies; 3D ultrasound; magnetic resonance imaging; hysterosalpingography; hystero-laparoscopy

IMPACT OF THE FIRST-TRIMESTER PREECLAMPSIA SCREENING TEST ON THE OUTCOME OF PREGNANCY

GURANDA OKROPIRIDZE,^{1,2} ARSEN GVENETADZE, MD, PhD;² REVAZ SULUKHIA, MD, PhD;³ RUSUDAN GVENETADZE, MD, PhD²

¹ Tbilisi State University, Tbilisi, Georgia

² Zurab Sabakhtarashvili Reproductive Clinic, Tbilisi, Georgia

³ Gudushauri National Medical Center, Tbilisi, Georgia

ABSTRACT

Context: Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide.

Objective: To assess the effectiveness of the first-trimester preeclampsia screening test.

Materials and Methods: A prospective observational study was conducted in 143 pregnant women with confirmed high risk of preeclampsia (group I) at the Zurab Sabakhtarashvili Reproductive Clinic in 2020-2024. Among them, 99 had a diagnosis of infertility, and 44 did not have infertility. All participants underwent a preeclampsia screening test in the first trimester at 11-14 weeks of pregnancy, which included uterine artery Doppler, mean arterial pressure, and biochemical markers. High-risk pregnant women were treated with 150 mg of acetylsalicylic acid throughout the pregnancy. Also, in 2023-2024, 106 pregnant women who developed preeclampsia (group II) were studied at the Gudushauri National Medical Center. Logistic regression was used to exclude confounding factors.

Results: In 2020-2025, 950 preeclampsia screening tests were performed at ZSRC, according to which 503 cases were confirmed to be at high risk (53.4%). 143 pregnant women with high risk of preeclampsia were selected, and a prospective observational study was conducted. 90.2% of them did not develop preeclampsia, and 9.8% (14 pregnant women) developed preeclampsia. It should be noted that no problems with maternal or fetal health were observed in these patients (maternal mortality – 0, fetal mortality – 0, hysterectomy – 0, maternal intensive care unit placement – 0). In addition, we studied 106 pregnant women who developed preeclampsia. It is noteworthy that they did not undergo a screening test. In these pregnant women, fetal death occurred in 13 (12.3%), hysterectomy in 5 (4.7%), and maternal intensive care unit placement in 5 (4.7%). The difference in maternal and fetal adverse outcomes between the screened and unscreened groups was significant ($p < 0.05$).

Conclusion: The study results show that 90.2% (129) of women at high risk of preeclampsia with the first-trimester preeclampsia screening test who were given 150 mg of acetylsalicylic acid did not develop preeclampsia, and 9.8% (14) of those who developed preeclampsia did not experience any maternal or fetal health complications. Maternal and fetal morbidity – 0, hysterectomy – 0.

These results demonstrate the effectiveness of this test.

Keywords: preeclampsia; infertility; pregnancy complications; maternal health, screening test

THE ROLE OF GABAERGIC DYSREGULATION IN PCOS AND FHA: SHARED NEUROENDOCRINE PATHWAYS AND DIVERGENT CLINICAL MANIFESTATIONS

MARIAMI ANDGULADZE, MD, PhD;¹ GEORGE TEVDORASHVILI, MD, PhD²

¹ Medicare Georgia, Tbilisi, Georgia

² First University Clinic, Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Background: γ -aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system, which plays a vital role in modulating the activity of hypothalamic GnRH neurons, thereby influencing the neuroendocrine regulation of reproductive function. Recent studies have highlighted the pathological modulation of GABAergic activity in both polycystic ovary syndrome (PCOS) and functional hypothalamic amenorrhea (FHA). Both disorders are characterized by changes in hypothalamic GnRH secretion, although in each case, we find different mechanisms underlying these changes.

Objective: The aim of the review is to evaluate the role of GABAergic signaling in PCOS and FHA, to explore and compare common and distinct neuroendocrine mechanisms, to highlight clinical significance, and to discuss therapeutic perspectives.

Methods: An analysis of the available literature (PubMed, Scopus, Web of Science), including a review of recent experimental and clinical studies, was conducted, focusing on GABAergic modulation of GnRH pulsatility in the context of PCOS and FHA. Particular attention was paid to the interaction between GABA, kisspeptin, and neurosteroids.

Findings: In both PCOS and FHA, GABA dysregulation is a mediator in the development of hypothalamic dysfunction involving the GABAergic-kisspeptin network; however, the mechanisms – hyper vs. hypoactivity – differ.

Conclusions: Imbalance of the GABAergic system represents a common neurobiological framework in the pathogenesis of PCOS and FHA. The different neuroendocrine responses highlight the need to address the specific state of GABAergic tone in the treatment of reproductive dysfunction. Potential therapeutic targets include the use of GABA-A modulators, inositol, and neurosteroid agents. This knowledge highlights the need for individualized therapeutic strategies, suggesting new directions for research, including targeting neuromediator networks in the management of reproductive dysfunction, the need for future development of targeted neuromodulatory therapies, and the need to improve personalized approaches to reproductive endocrine disorders.

Keywords: GABA; PCOS; FHA; GnRH; neuroendocrinology; HPG axis; DHEA; stress; neurosteroids

ENDOCRINE-METABOLIC PANEL IN PUBERTAL DEVELOPMENT DISORDERS

**SHOTA JANJGHAVA, MD, PhD; ELENE GIORGADZE, MD;
NINO SIKHARULIDZE, MD; REVAZI JAMBURIA, MD**
National Institute of Endocrinology, Tbilisi, Georgia

ABSTRACT

Background: Pubertal development is a neuroendocrine process with physiological changes and maturation, typically assessed using Tanner stages. Genetic predisposition plays a significant role in pubertal timing, but recent findings highlight the complex interplay of nutrition status and endocrine-disrupting chemicals (EDCs) on pubertal timing. EDCs are exogenous chemicals or compounds with different half-lives and long-term effects. EDCs can interfere with endogenous hormone action by binding to receptors, affecting their synthesis, transport, metabolism, or elimination.

Results: To identify its effect on pubertal development, various EDCs, including agricultural pesticides, industrial chemicals, flame retardant chemicals, organic compounds, phthalates, persistent organic pollutants, tobacco smoke, metals, dietary consumption, and restrictions, were studied in different countries using different methods. Researches reveal that substances above can mimic/enhance estrogen activity, interfere with male hormones, or have mixed effects, through which they may affect pubertal development. Although complex research is still needed to identify the individual effects of EDCs, as humans are exposed to multiple chemicals at some point, this could blur the borders.

Conclusion: Along with patient history, genetic predisposition, and a comprehensive endocrine-metabolic panel, it is wise to consider potential environmental exposures in adolescents, as numerous EDCs have been identified to affect pubertal development, ranging from precocious to delayed puberty and sexual differentiation disorders.

Keywords: pubertal development disorders, precocious puberty, pubertal delay, endocrine-disrupting chemicals.

THE ROLE OF THE VEGETATIVE NERVOUS SYSTEM IN THE DEVELOPMENT OF REPRODUCTIVE FUNCTION DISORDERS IN CHILDREN OF MOTHERS TREATED FOR POLYCYSTIC OVARY SYNDROME

RUSUDAN JASHI, MD, PhD

*Academic V. Iverieli Endocrinology, Metabology, and Dietology Center "ENMEDIC";
Georgian Society of Clinical Pharmacology "Primum Non Nocere" (PNN), Tbilisi, Georgia*

ABSTRACT

Background: Recent advances in endocrine treatment have improved infertility outcomes for women with polycystic ovary syndrome (PCOS). However, concerns remain about the long-term effects on the offspring of these women, particularly regarding reproductive and neuroendocrine development.

Objective: To evaluate the functional state and risk of reproductive dysfunction in children born to mothers treated for infertility due to PCOS.

Materials and Methods: The study involved 153 children aged 0-18 years. The leading group included 77 children born to mothers with PCOS who underwent wedge resection surgery. A control group of 76 children was selected from healthy mothers without a history of infertility. Clinical and paraclinical assessments were conducted, including anthropometry, laboratory tests (blood, urine, feces), ECG, FCG, chest fluorography, EEG, hormonal profiles, genital and adrenal ultrasound, and evaluations by pediatricians, neurologists, endocrinologists, and other specialists.

Results: Children of mothers with PCOS demonstrated a high incidence of reproductive and neuroendocrine disorders. Findings included delayed pubertal development, menstrual irregularities, increased gonadotropic hormone levels (88.9%), and absence or delay in secondary sexual characteristics (11.3% of cases). Many showed signs of vegetative dystonia, including emotional instability, blood pressure fluctuations, fatigue, and night terrors. These abnormalities are believed to have genetic or prenatal origins and were significantly more prevalent compared to the control group.

Conclusions: Children born to mothers with PCOS treated for infertility are at increased risk of reproductive dysfunction and autonomic nervous system disturbances. Since the reproductive system shares mechanisms with other functional systems (cardiovascular, respiratory, etc.), it is necessary to develop a complex therapy aimed at both restoring reproductive function and normalizing autonomic nervous system disorders. Early preventive and therapeutic interventions are recommended to mitigate long-term consequences and support healthy development.

Keywords: polycystic ovary syndrome; reproductive dysfunction; children; vegetative dystonia; hormonal imbalance



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MATERNAL MEDICATION AND NEONATAL RISK: THE CASE FOR DIGITAL INTEGRATION

RUSUDAN JASHI, MD, PhD^{1,2}

¹ Academic V. Iverieli Endocrinology, Metabology, Dietology Center ENMEDIC, Tbilisi, Georgia

² Georgian Society of Clinical Pharmacology and Rational Pharmacotherapy Primum Non Nocere (PNN), Tbilisi, Georgia

ABSTRACT

Background: In Georgia, perinatal mortality represents a significant portion of infant deaths and reflects the quality of care provided to mothers and newborns. Medication use during pregnancy and delivery, especially among mothers previously treated for endocrine-related infertility, is a frequently overlooked factor affecting neonatal outcomes.

Objectives and Methods: This study aimed to identify medication-related risk factors in perinatal mortality. A retrospective pharmacological analysis of 225 neonatal deaths and their mothers' medical records was conducted, including cases involving prior treatment for endocrine infertility. Associations between maternal medication use and neonatal complications or mortality were analyzed.

Results:

- **Magnesium sulfate:** 11% of newborns demonstrated toxicity, including CNS depression.
- **Diazepam:** Maternal use during labor was associated with neonatal apnea and hypothermia in 9%.
- **Naphthyzinum:** One case of apnea and convulsions occurred following maternal use.
- **Nadroparin:** Two preterm twins developed elevated APTT and grade II intraventricular hemorrhage.

Conclusions: Maternal drug history – particularly in mothers previously treated for endocrine infertility – must be integrated into hospital information systems to improve neonatal drug safety. Digital pharmacovigilance tools and structured documentation can support clinical decision-making and reduce adverse outcomes.

Keywords: maternal medication; neonatal drug safety; perinatal mortality; digital integration; pharmacovigilance

NEUROENDOCRINE BACKGROUND OF FUNCTIONAL HYPOTHALAMIC AMENORRHEA (FHA)

BLAZEJ MECZEKALSKI, Prof.

*Department of Gynecological Endocrinology, Poznan University of Medical Sciences,
Poznan, Poland*

ABSTRACT

Three primary causes of functional hypothalamic amenorrhea have been identified as energy deficits, which are the result of either a reduced energy intake, excess exercise and stress as well as neuroendocrine disturbances in the pulsatile release of Gonadotropin-releasing hormone (GnRH). Oftentimes the underlying cause for the incidence of Functional hypothalamic amenorrhea (FHA) is a combination of the three factors. Considering the link established between stress reactions in women and the incidence of FHA, the neuroendocrine agents involved in regulating the hypothalamic-pituitary-adrenal axis (and so the levels of CRH, ACTH and cortisol and the severity of stress reactions) are considered to have a considerable potential to alter the incidence and evolution of FHA in women.

One of the most important neuropeptide involved in pathophysiology of FHA is kisspeptin. From the physiological point of view kisspeptin is the main positive regulator of GnRH pulsatility. Patients with FHA are characterized by lower serum kisspeptin levels and reduced kisspeptin pulsatility.

Neuropeptide Y, a neuroendocrine transmitter widespread across many systems in the body plays a significant role in the management of stress reactions. NPY is one of the agents that stimulates the release of GnRH.

Another regulator that is strongly linked with stress reactions and can heavily influence the function of the hypothalamic-pituitary-gonadal (HPG) axis is melatonin. Decreased melatonin concentrations not only can promote the activation of the hypothalamic-pituitary-adrenal (HPA) axis, but also potentially have a negative effect on ovarian function, seeing as high melatonin levels have been identified locally in follicular fluid of the ovaries.

Allopregnanolone is yet another regulator of stress alleviation. It is a product of the metabolism of progesterone. It modulates the function of the γ -Aminobutyric acid type A (GABAA) receptor by allosteric binding.

Similarly, beta-endorphins, a group of peptides secreted widely across the body which acts as agonists to opioid receptors, have been found to ameliorate stress reactions and overall to

support the restoration of homeostasis when the organism is exposed to stressful conditions. Because disturbances in energy supply play such a crucial role in development and progression of FHA, many neurohormonal agents which regulate food intake, such as insulin, leptin and ghrelin, are also involved in modulating GnRH release.

Keywords: functional hypothalamic amenorrhea (FHA); gonadotropin-releasing hormone (GnRH); kisspeptin; neuropeptide Y (NPY); melatonin; stress and energy balance

PCOS IN ADOLESCENTS: CURRENT VIEW

BLAZEJ MECZEKALSKI, Prof.

*Department of Gynecological Endocrinology, Poznan University of Medical Sciences,
Poznan, Poland*

ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. A diagnosis of PCOS is established when a patient exhibits two of three Rotterdam criteria: oligoovulation or anovulation, excess androgen activity, and polycystic ovarian morphology. The dynamic physiological and anatomical changes which occur in puberty make for a challenging diagnosis in this group of patients. It is important to be mindful of the physiological particularities in adolescence which often mimic the symptoms of PCOS. In their first-year post-menarche, approximately 75% of menstruating adolescents report their cycle to last between 21-45 days. Recent studies have shown that regular menstrual cyclicity is only achieved within 2-3 years post-menarche. Anovulation, as a crucial diagnostic element for PCOS, features in about half of early-post-menarchal adolescents. Hirsutism and acne are the most common clinical manifestations of hyperandrogenism, and mild features are developed by most adolescents as a result of elevated androgen levels. Distinguishing between a pathological sign and normal features of maturation is often difficult. A polycystic ovarian morphology (PCOM) through ultrasound has been found in up to 40%, 35%, and 33.3% of patients when assessed at 2, 3, and 4 years, respectively, after menarche. International guidelines recommend against the use of pelvic ultrasound until 8 years post-menarche. The primary aim of management is focused mainly on improving hormonal and metabolic status, the prevention of future comorbid complications, and generally improving the overall quality of life in young women with PCOS. Considerable controversy surrounds the choice of optimal pharmacological treatment to address PCOS in adolescents. There is a lack of robust and reliable trials in the literature addressing the use of combined oral contraceptives. Further work needs to be undertaken in order to provide safe and effective care to the adolescent population in this regard.

Keywords: polycystic ovary syndrome (PCOS); adolescence; Rotterdam criteria; hyperandrogenism; polycystic ovarian morphology (PCOM); menstrual irregularities

NEW APPROACHES TO THE MANAGEMENT OF PREGNANT WOMEN WITH ANTIPHOSPHOLIPID SYNDROME (APS) AND GENETIC THROMBOPHILIA AGAINST THE BACKGROUND OF MYELOPROLIFERATIVE DISEASES (MPD)

ARCHIL KHOMASURIDZE, MD, PhD, Prof.;^{1,2} **MARINA JANGIDZE**, MD³

¹ Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

² The Head of the Department of Reproductology, Obstetrics and Gynecology at Ivane Javakhoshvili Tbilisi State University, Tbilisi, Georgia

³ Alexandre Aladashvili University Clinic, Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Background: In recent years, an increase in MPD among pregnant women with APS and genetic thrombophilia **has resulted** in a greater risk of thrombotic and obstetric complications, requiring the development of a special approach to pregnancy, delivery, and the postpartum period.

Objective: To study pregnancy management in women with APS and genetic thrombophilia against the background of MPD – essential thrombocythemia (ET) and polycythemia vera (PV) – and to develop recommendations for pregravid preparation, pregnancy, delivery, and postpartum management.

Materials and Methods: Peripheral blood test with platelet count, coagulogram with platelet aggregation, D-dimer, LA, ACA, homocysteine, mutations: FV (Leiden), prothrombin, AT-III, PrC.

Results: In 20 pregnant women with MPD aged 22-41 years, 15 had ET and 5 had PV. Pregnancy duration ranged from 4 to 38 weeks. The study of the hemostasis system indicated activation of hemostasis from the early stages of gestation (6-7 weeks). In 6 women with ET and 3 with PV, intensification of intravascular blood coagulation was noted at 18-20 weeks of gestation, resulting in increased D-dimer, platelet count, platelet aggregation, and homocysteine; circulation of high titers of LA and ACA in the blood; and decreased AT-III and PrC. All women were given anticoagulant therapy with LMWH, antiplatelet therapy with aspirin, and cytoreductive therapy with pegylated interferon-2a, which allowed pregnancy prolongation and prevention of thrombotic and obstetric complications.

Conclusion: Despite various forms of MPD (ET, PV), all pregnant women experienced early activation of the hemostasis system combined with intensification of intravascular blood coagulation, which creates a risk of thrombotic and obstetric complications, especially in combination with APS and genetic thrombophilia. Therapeutic approaches to these conditions remain the same: anticoagulant, antiplatelet, and cytoreductive therapy in the pregravid period and throughout pregnancy, delivery, and the postpartum period.

Keywords: lupus anticoagulant; antiphospholipid syndrome; anticardiolipin antibodies; essential thrombocythemia; polycythemia vera

BARDET-BIEDL SYNDROME PRESENTING WITH ABNORMAL UTERINE BLEEDING: A CASE REPORT

MARIAM RAMISHVILI;¹ ELISABED PKHALADZE;¹ NINO DAVIDOVA;² LALI PKHALADZE²

¹ DTMU, Tbilisi, Georgia

² Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, polydactyly, central obesity, cognitive impairment, renal anomalies, and hypogonadism. Irregular menstrual cycles are frequently observed in affected individuals, though the occurrence of abnormal uterine bleeding is an uncommon and complex clinical manifestation.

Case Presentation: We describe the case of a 22-year-old female with genetically confirmed Bardet-Biedl Syndrome, diagnosed at age 10, who presented with refractory abnormal uterine bleeding. Menarche occurred at 16 years, followed by persistent menstrual irregularities, including oligomenorrhea, secondary amenorrhea, and menometrorrhagia – heavy and prolonged uterine bleeding occurring both at the expected time of menstruation and at irregular intervals between periods. She was born at term with polydactyly of both hands and feet, which was surgically corrected in infancy. Her medical history included childhood-onset obesity and progressive visual impairment from age 10. Additional clinical features included developmental delay, speech deficits, dental anomalies, ataxia, central obesity (BMI: 40 kg/m²), hirsutism, and hyperinsulinemia. Pelvic ultrasonography revealed a bicornuate uterus, while the urinary tract appeared normal. Despite multiple treatment regimens – including combined oral contraceptives, norethisterone, dydrogesterone, and tranexamic acid – bleeding remained uncontrolled. Endometrial thickness fluctuated between 5 and 15 mm. Amenorrhea was effectively induced as a therapeutic measure through the administration of a GnRH agonist. Adjunctive therapy included vitamin D supplementation and metformin for insulin resistance.

Conclusion: This case highlights the multifactorial nature of menstrual disturbances in Bardet-Biedl Syndrome, where structural uterine anomalies and metabolic and neuroendocrine abnormalities collectively contribute to abnormal uterine bleeding. Conventional treatments may be insufficient, necessitating an individualized management approach. Increased awareness of the gynecological manifestations of BBS is critical for improving the quality of life in affected individuals.

Keywords: Bardet-Biedl Syndrome, abnormal uterine bleeding, irregular menstrual cycle, metabolic and neuroendocrine abnormalities, GnRH agonists

THE EFFECT OF IMMUNOTHERAPY IN REPRODUCTIVE MEDICINE

NATALIA RUSAKOVA, MD; IRINA GOGOKHIA, MD; TAMAR DIAKONIDZE, MD
Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Immunotherapy is an emerging adjunctive strategy in reproductive medicine, particularly for patients with immunologically mediated infertility or recurrent pregnancy loss. This study explores the clinical application and outcomes of immunotherapy using allogeneic lymphocytes derived from the male partner, integrated into a broader treatment protocol for thrombophilia-associated reproductive complications.

Methods: A standardized treatment regimen – comprising low-molecular-weight heparin, natural progesterone, folic acid, magnesium, vitamin therapy (including omega-3 fatty acids), and paternal lymphocyte immunotherapy – was implemented between 2018 and 2022. A prospective study involved 598 women aged 18-40 years with histories of recurrent pregnancy loss and failed assisted reproductive procedures. Of these, 398 received lymphocyte immunotherapy.

Results: The treatment group demonstrated a significantly higher pregnancy success rate (**89.9%**) compared with those managed with conventional therapies alone (**37%**). Furthermore, 297 women who received immunotherapy during early gestation as part of a combined therapeutic protocol all achieved full-term physiological childbirth. In a recent cohort of 71 patients undergoing IVF with complex obstetric histories, 67 delivered healthy infants following lymphocyte immunotherapy.

Conclusions: These findings underscore the therapeutic potential of lymphocyte immunotherapy in enhancing implantation and pregnancy success, particularly in patients with unexplained infertility, recurrent miscarriage, or IVF failure. Continued investigation and standardization of treatment protocols are warranted to expand its clinical application within reproductive medicine.

Keywords: reproductive immunology; lymphocyte immunotherapy; recurrent pregnancy loss; IVF failure; thrombophilia; maternal-fetal tolerance; alloimmune response

HORMONAL INTERFERENCE: UNVEILING THE ADOLESCENT SPECTRUM OF HYPERPROLACTINEMIA

SALOME SABULUA, MD

Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Hyperprolactinemia (HPrl), with a reported prevalence of 0.4-5% in adult women, occurs less commonly in adolescents but may exert profound effects on growth, pubertal progression, and reproductive health. Elevated prolactin (PRL) levels disrupt the hypothalamic-pituitary-ovarian (HPO) axis, leading to delayed puberty, menstrual irregularities, and ovulatory dysfunction. In adolescents, the clinical presentation is often subtler and more variable than in adults, making early recognition and diagnosis particularly challenging.

Objective: To outline the unique clinical characteristics, diagnostic challenges, and management strategies of hyperprolactinemia in adolescents, with emphasis on its significance for long-term reproductive, skeletal, and metabolic health.

Materials and Methods: A narrative review of existing literature and clinical cases was conducted, focusing on the causes of hyperprolactinemia in adolescents – including tumor-related, functional, and iatrogenic origins – along with diagnostic challenges and therapeutic approaches.

Results: Hyperprolactinemia in adolescents may arise from multiple causes. Iatrogenic HPrl is frequently associated with medications such as antipsychotics and selective serotonin reuptake inhibitors (SSRIs). Although less common in this population, prolactinomas may produce significant clinical symptoms due to tumor mass effects and markedly elevated prolactin levels. Functional HPrl generally leads to mild-to-moderate increases in prolactin and may be accompanied by polycystic ovarian morphology or hirsutism. Key diagnostic challenges include macroprolactinemia and the hook effect, which can complicate accurate prolactin measurement. Magnetic resonance imaging (MRI) with gadolinium contrast remains the gold standard for identifying sellar lesions. Dopamine agonists, particularly cabergoline, are the preferred treatment due to their efficacy and favorable tolerability. The hypogonadotropic state induced by HPrl may impair peak bone mass acquisition during adolescence, posing potential long-term risks to skeletal health.

Conclusions: Early recognition and individualized evaluation of HPrl in adolescents are crucial. Prolactin level assessment is recommended in patients presenting with delayed puberty, menstrual disturbances, growth abnormalities, or obesity. Timely diagnosis combined with ongoing monitoring is vital to prevent adverse reproductive, skeletal, and metabolic outcomes.

Keywords: hyperprolactinemia; adolescents; prolactinoma; pubertal delay; dopamine agonists

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ADROGEN RECEPTOR EXPRESSION IN OVARIAN AND BREAST EPITHELIAL CANCERS AND ITS ASSOCIATION WITH PROLIFERATION, APOPTOSIS, AND CANCER STEM CELL FEATURES

KETEVAN SHENGELAIA, MD, PhD Student^{1,2,3}

¹ *Gagua Clinic, Tbilisi, Georgia*

² *Ken Walker Clinic, Invited Lecturer, Tbilisi, Georgia*

³ *Med Diagnostics, Tbilisi, Georgia*

ABSTRACT

Background: The androgen receptor (AR), though extensively studied in prostate cancer, has recently gained attention in female malignancies. In ovarian and breast epithelial cancers, AR influences hormonal responsiveness, tumor growth, apoptotic regulation, and cancer stem cell (CSC) behavior. Its clinical value remains under investigation, particularly regarding prognosis and treatment resistance.

Objective: To systematically evaluate the expression and biological significance of AR in epithelial ovarian and breast cancers, and to analyze its association with cellular proliferation, apoptosis, CSC marker expression, hormone receptor profiles, therapeutic resistance, and clinical outcomes.

Materials and Methods: A systematic review was performed using PubMed and ScienceDirect. Twenty-six peer-reviewed articles with DOIs were included, each assessing AR in relation to tumor biology or clinical parameters. Studies examined proliferation, apoptosis, CSC markers (*CD44*, *ALDH1*), estrogen and progesterone receptor expression, chemotherapy response, and survival outcomes. Findings were synthesized through thematic analysis across histologic subtypes.

Results: AR demonstrates context-specific activity. In serous ovarian cancer, a low AR/progesterone receptor ratio is linked with poor prognosis. In ER-positive breast cancer, AR may mitigate estrogen-driven signaling, whereas in triple-negative breast cancer (TNBC), AR expression correlates with enhanced tumor growth and stemness through PI3K/AKT and Wnt/ β -catenin pathways. Elevated AR levels are associated with reduced apoptosis, increased CSC marker expression, and chemotherapy resistance, particularly in ER-low/AR-high tumors.

Conclusions: AR represents a clinically relevant factor in ovarian and breast cancers, shaping tumor progression, stemness, and treatment resistance. AR profiling may support personalized treatment strategies. AR-targeted agents, such as enzalutamide, show early promise – especially in combination regimens – and warrant further clinical evaluation.

Keywords: androgen receptor; ovarian cancer; breast cancer; cancer stem cells; hormone resistance

UTERINE RECONSTRUCTION FOLLOWING NEAR-COMPLETE TRANSECTION DURING MYOMECTOMY: IMPLICATIONS FOR CONGENITAL REPAIR

RAMAZ CHAREKISHVILI, MD, PhD; DAVID SKHIRTADZE, MD, MPH, PhD; IA SHUKASHVILI, MD
Department of Endoscopic Gynecologic Surgery, Clinic Caraps Medline, Tbilisi, Georgia

ABSTRACT

Background: Laparoscopic myomectomy for large fibroids carries a significant risk of intraoperative complications, including vascular injury and extensive disruption of uterine anatomy. In patients desiring future fertility, uterine preservation is paramount. This case illustrates successful laparoscopic uterine reconstruction following near-complete transection of the uterine body and explores its potential application in the surgical management of selected congenital uterine anomalies (CUAs).

Objective: To report a case of major supracervical uterine transection with unilateral uterine artery injury during laparoscopic myomectomy and describe the successful laparoscopic reconstruction, emphasizing fertility preservation and possible implications for CUA repair.

Materials and Methods: A 35-year-old woman underwent laparoscopic myomectomy for a large FIGO type 2-5 fibroid (**15.0-20.0 cm**), circumferentially involving the supracervical region. During enucleation, an inadvertent transection of the left uterine vessels and approximately 90% of the supracervical uterine body occurred. The remaining uterine tissue was suspended from the left broad ligament via a narrow residual supracervical bridge. Reconstruction involved insertion of an 8.5-mm Hegar dilator into the cervical canal to support anatomical alignment. The endometrial layer was approximated with a circular suture, followed by interrupted suturing of the myometrial and serosal layers. Uterine perfusion was preserved through the left uterine artery and residual tissue bridge.

Results: Reconstruction was completed laparoscopically without conversion to laparotomy. Estimated blood loss was 600 mL, and operative time was 170 minutes. Postoperative recovery was uneventful, with no hematometra or stricture formation observed. At 8-week follow-up, transvaginal ultrasound confirmed normal uterine contour and perfusion. The patient resumed regular menstruation without complications.

Conclusions: This case demonstrates that even in the setting of near-complete uterine transection and unilateral vascular injury, laparoscopic reconstruction may effectively restore uterine integrity and preserve reproductive potential. Such techniques may also offer promise for selected patients with CUAs amenable to surgical repair.

Keywords: myomectomy; uterine reconstruction; fertility; congenital uterine anomalies (CUA)

FROM PRENATAL DIAGNOSIS TO POSTNATAL SURGERY: A CASE OF GIANT FETAL OVARIAN CYST REQUIRING NEONATAL INTERVENTION

ANA GHVINIASHVILI, MD, PhD Candidate;^{1,2} **NATA NAKAIDZE**, MD, BA;²

SALOME SABULUA, MD;² **NANA CHOPIKASHVILI**, MD, PhD²

¹ PhD Candidate, New Vision University, Tbilisi, Georgia

² Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Fetal ovarian cysts are the most common prenatally detected intra-abdominal masses in female fetuses, with an incidence of approximately 1 in 2,500 live births. While typically benign and self-resolving, large or complex cysts may result in torsion, rupture, or hemorrhage. The predominant theory attributes their formation to fetal ovarian hyperstimulation, driven by elevated maternal and placental hormones such as human chorionic gonadotropin (hCG) and estrogens.

Objective: To highlight the necessity of neonatal surgical intervention by presenting a rare case of a giant fetal ovarian cyst and to review current diagnostic and therapeutic strategies.

Materials and Methods: At 36 weeks of gestation, routine ultrasound revealed a 3-cm left ovarian cyst, which rapidly enlarged to 10 cm. This was the mother's second spontaneous, naturally conceived, and physiological pregnancy, without ovulation induction or assisted reproductive technologies. At 40 weeks, cesarean section was performed. A 3400-g female neonate was delivered, presenting with pronounced abdominal distension and signs of intestinal compression. On postnatal day two, laparotomy revealed a giant left ovarian cyst with cystic degeneration. The cyst was aspirated (200 mL of clear fluid), and the necrotic ovarian tissue was excised. Histopathological examination confirmed a benign follicular cyst.

Results: Surgical intervention was warranted due to the cyst's size and compressive effects. Follow-up ultrasonography at 2, 5, and 7 months confirmed preservation of the left ovary, which appeared hypoplastic but measurable (0.6 mL). The right ovary showed several simple follicular cysts (up to 9 mm). Hormonal assays, including prolactin, thyroid panel, and estradiol, were normal, reducing suspicion of underlying endocrine disorders. At 7 months, the infant displayed age-appropriate female external genitalia, with minor posterior labial synechiae. Given the cysts' tendency to regress, the next follow-up was scheduled in 3 months.

Conclusion: This case illustrates the importance of prompt detection and management of rapidly enlarging fetal ovarian cysts, which can pose significant postnatal risks. Early diagnosis, consistent prenatal monitoring, and timely surgical intervention are key to preserving ovarian tissue and function, even in cases requiring neonatal surgery. Long-term follow-up is essential for evaluating contralateral ovarian development and future reproductive potential.

Keywords: fetal ovarian cyst; giant ovarian cyst; prenatal diagnosis; follicular cyst; neonatal surgery

THE USE OF HYALURONIC ACID GEL TO PREVENT INTRAUTERINE ADHESION AFTER INTRAUTERINE OPERATIONS

LILIT KALASHYAN, MD; ARTUR SARKISOV, MD

ABSTRACT

Background: Intrauterine adhesion (IUA) is a severe complication that can occur following abortion or other intrauterine operations. Hyaluronic acid gel has been investigated as a preventive strategy to reduce the risk of IUA after intrauterine procedures.

Objective: To systematically evaluate the efficacy of hyaluronic acid gel in preventing IUA following intrauterine operations.

Methods: A meta-analysis was conducted, including seven randomized controlled trials with 952 patients who underwent intrauterine operations. The analysis indicated that hyaluronic acid gel significantly reduced the incidence of IUA [relative risk (RR)=0.42; 95% confidence interval (CI)=0.30-0.57; $p<0.001$] and lowered IUA severity scores (mean difference = -1.29 ; 95% CI = -1.73 to -0.84 ; $p<0.001$). Subgroup analysis demonstrated that the preventive effect was consistent across types of intrauterine operations, including abortion (RR=0.40; 95% CI=0.26-0.62; $p<0.001$) and hysteroscopy (RR=0.44; 95% CI=0.28-0.68; $p<0.001$).

Results: The protective effect of hyaluronic acid gel was not influenced by the underlying condition, including abortion (RR=0.48; 95% CI=0.29-0.78; $p=0.003$), IUA (RR=0.38; 95% CI=0.21-0.67; $p<0.001$), and submucosal myoma, endometrial polyps, or mediastinum uterus (RR=0.40; 95% CI=0.18-0.90; $p=0.03$). Additionally, hyaluronic acid gel was associated with improved pregnancy rates after intrauterine operations (RR=1.94; 95% CI=1.46-2.60; $p<0.001$).

Conclusion: Hyaluronic acid gel significantly reduces the incidence and severity of intrauterine adhesions following intrauterine operations, independent of the type of procedure or underlying pathology. Moreover, treatment with hyaluronic acid gel improves pregnancy outcomes, supporting its use in postoperative management.

Keywords: intrauterine adhesion; hyaluronic acid gel; intrauterine operation; hysteroscopy; prevention.

ლიდერ გრუპი



RECONSTRUCTION OF THE FALLOPIAN TUBE USING OFFICE MINI-HYSTEROSCOPY DURING INFERTILITY TREATMENT

**MANANA MGALOBlishvili, MD¹; ANTON MGALOBlishvili, MD¹;
NINO VARDOSANIDZE, MD¹; NATA NAKAIDZE, MD²**

¹ Manana Mgaloblishvili Center for Reproductive Medicine, Tbilisi, Georgia

² Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Obstruction of the fallopian tubes accounts for **30%-40%** of female infertility cases and may occur at various segments along the tubes. The proximal tubal ostium is involved in **approximately 10%-25%** of these cases, presenting significant challenges for successful conception. Conventional diagnostic and therapeutic modalities are often invasive or have limited accessibility. Office-based mini-hysteroscopy represents a minimally invasive, cost-effective alternative, enabling direct visualization and reconstruction of the tubal ostium, with potential to enhance fertility outcomes.

Objective: To evaluate the efficacy of office-based mini-hysteroscopy in the treatment of proximal tubal ostial obstruction and in restoring fallopian tube patency during infertility treatment.

Materials and Methods: A retrospective study was conducted on patients who presented at the **Manana Mgaloblishvili Center for Reproductive Medicine**. The study cohort consisted of **27 patients (mean age, 33 ± 5 years)** diagnosed with fallopian tube obstruction or narrowing based on sonosalpingography findings. Mini hysteroscopy was subsequently performed, revealing tubal pathologies such as adhesions and polyps. **Surgical reconstruction of the tube was performed, and tubal patency was reassessed.**

Results: A statistically significant improvement in tubal patency was observed in **70.4% (n=19; P<.05)**. In 7 patients, tubal patency remained unchanged despite treatment. Within 6 months following the procedure, pregnancy was achieved in **25.9% (n=5)**.

Conclusions: Mini-hysteroscopy is a minimally invasive technique that facilitates direct visualization and accurate diagnosis of tubal pathologies while enabling therapeutic intervention through tubal reconstruction. This approach offers a promising, cost-effective, outpatient-based alternative that may improve fallopian tube patency and fertility outcomes. **Further large-scale studies are warranted to confirm its long-term efficacy and safety in the management of tubal obstruction.**

Keywords: mini-hysteroscopy; fallopian tube obstruction; tubal patency; infertility treatment

LATENT COMPLICATIONS FOLLOWING CONSERVATIVE MYOMECTOMY IN AN IVF PATIENT - A CASE PRESENTATION

NATIA PKHALADZE, MD, PhD;¹ LANA EZIESHVILI, MD;² SOPHIA TAMAZASHVILI, MD;^{1,3}

¹ Department of Obstetrics and Gynecology, Tbilisi State Medical University, First University Clinic, Tbilisi, Georgia

² Department of Radiology, Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia

³ David Davarashvili Clinic, Tbilisi, Georgia

ABSTRACT

Background: Patients undergoing IVF often represent a high-risk cohort due to advanced maternal age, infertility-related comorbidities, and previous uterine interventions. A multidisciplinary approach involving obstetricians, neonatologists, and surgical teams is essential to ensure optimal maternal and fetal outcomes.

Case Presentation: We describe a 46-year-old gravida 2, para 0 woman at 27 weeks of gestation, conceived via in vitro fertilization (IVF), with a history of two laparoscopic conservative myomectomies. Regular antenatal follow-ups demonstrated normal fetal growth and placental development. The current pregnancy had been uneventful, with normal fetal growth and placental localization on prior scans. There was no history of uterine pain, contractions, or bleeding during this hospitalization. She conceived via IVF due to age-related subfertility and a uterine factor likely secondary to fibroid-related distortion.

During hospitalization, the patient received treatment for threatened preterm labor according to national protocol in Georgia, including tocolytic therapy, fetal respiratory distress syndrome (RDS) prophylaxis, and dynamic monitoring.

On the third day of hospitalization, a follow-up transabdominal ultrasound was performed as part of standard discharge planning. Unexpectedly, imaging revealed partial separation of the amniotic sac from the uterine wall, with herniation through a defect in the anterior fundal myometrium into the abdominal cavity. The fetus remained confined within the uterine cavity. Fetal biometric measurements were appropriate for gestational age, and the placenta was usually positioned. However, the fetal biophysical profile (BPP) was 4/10.

The patient underwent an emergency laparotomy with total hysterectomy due to the extent of the uterine rupture and the friable, irreparable condition of the remaining myometrial tissue.

The estimated intraoperative blood loss was moderate and managed effectively with transfusion support.

Outcomes: Maternal: Uneventful recovery post-hysterectomy. Neonate: Stable post-delivery, admitted to NICU, no intubation required.

Conclusion: This case underscores the need for individualized surveillance in IVF pregnancies post-myomectomy. Routine imaging, even in asymptomatic patients, can identify life-threatening complications early. High clinical suspicion and multidisciplinary readiness are key to reducing maternal and fetal morbidity.

Keywords: conservative myomectomy; IVF pregnancy; uterine rupture; uterine scarring; assisted reproductive technology; obstetric complications

FETAL EDEMA IN IVF PREGNANCY - ANTENATAL DIAGNOSIS AND MANAGEMENT: A CASE REPORT

NATIA PKHALADZE, MD, PhD;¹ LANA EZIESHVILI, MD;² SOPHO TAMAZASHVILI, MD^{1,3}

¹ Department of Obstetrics and Gynecology, Tbilisi State Medical University,
First University Clinic, Tbilisi, Georgia

² Department of Radiology, Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia

³ David Davarashvili Clinic, Tbilisi, Georgia

ABSTRACT

Background: Non-immune hydrops fetalis (NIHF) is characterized by the accumulation of excess fluid in fetal tissues and cavities, often caused by cardiac, chromosomal, infectious, or metabolic abnormalities. In many cases, however, the cause remains idiopathic.

Case Description: We report the case of a 20-year-old primigravida with an IVF-conceived pregnancy at 31 weeks of gestation who presented with ultrasound findings of fetal edema, ascites, and skin thickening. Despite an extensive diagnostic workup, no definitive etiology was identified. The patient had not been under close antenatal care at our institution and reported no prior complications or documented investigations.

High-resolution obstetric ultrasound demonstrated peritoneal ascites (7 mm), subcutaneous edema (13-21 mm), and generalized skin thickening. Serologic, genetic, and cardiac evaluations were unremarkable, leading to a diagnosis of idiopathic NIHF.

Due to progressive fetal deterioration observed on serial biophysical and Doppler assessments, an elective cesarean section was performed at 31 weeks. The decision was guided by worsening fetal edema and multidisciplinary team recommendations, consistent with evidence supporting preterm delivery in severe cases.

The neonate (birth weight 1800 g) presented with marked skin edema, severe respiratory compromise, and poor Apgar scores. Intensive neonatal resuscitation was initiated, including mechanical ventilation, inotropic support, and fluid management. The infant's condition gradually improved, and he was discharged home after two months of NICU care.

Conclusion: This case underscores the diagnostic challenges of NIHF and highlights the importance of close antenatal surveillance, skilled ultrasound personnel, and comprehensive diagnostic workups to identify potential causes and guide management.

Keywords: fetal edema; IVF pregnancy; antenatal diagnosis; non-immune hydrops; fetal ultrasound; high-risk pregnancy

A SUCCESSFUL IVF PROCEDURE IN A WOMAN WITH A UNICORNUATE UTERUS. OUR CLINICAL EXPERIENCE

GUNAY SULTANOVA

IVF Unit, GenArt Clinic Mercan Hospital, Baku, Azerbaijan

ABSTRACT

Background: Unicornuate uterus is derived from unilateral Müllerian duct development, with the contralateral duct not or partially developing, and accounts for 5.0-20.0 % of all Müllerian anomalies [1]. Unicornuate uterus is one of the uterine anomalies that presents with obstetric [2]. In women with unicornuate uterus, the odds of achieving clinical pregnancy following one complete IVF-ICSI cycle were 24% lower, and the odds of live birth were 28% lower than in women with normal uterine anatomy after control for important demographic and clinical confounders [3]. Aim: To evaluate the impact of unicornuate uterus on perinatal outcomes after IVF according to the localization of embryo implantation.

Objective: Analysis of the characteristics and outcome of treatment in a woman with a unicornuate uterus who failed IVF in our experience.

Materials and methods of the study: A woman born in 1997 (30 years old) was diagnosed with a unicornuate uterus by ultrasound. The woman has been suffering from infertility for 4 years and has undergone one unsuccessful IVF operation. Her husband was diagnosed with oligospermia.

Results: Hysterosalpingography revealed a small uterus and one tube. Diagnostic laparoscopy revealed a diagnosis of unicornuate uterus. No rudimentary uterus was found. During primary hysteroscopy, the uterine cavity was expanded to the right side using sharp methods. Gel and balloons were placed. IVF was performed a month later. Two months later, one embryo from the obtained embryos was transferred during the transfer. A positive result was obtained. The placenta was located on the right lateral and right posterior walls. In the area of the placenta, some tissues were injured after hysterosalpingography.

Conclusion: Repeated implantation failures and spontaneous abortions are the most common indications for hysteroscopy during IVF. The causes of these can be eliminated at once by endoscopic visualization. From this point of view, hysteroscopy can be considered an integral part of IVF. In patients undergoing hysteroscopy due to suspected polyps measuring 5 mm or larger, complete or incomplete uterine cavity walls, thinned or inconsistent endometrium,

unicornuate uterus, or endometriosis, we can achieve successful transfer at the next stage by addressing these defects immediately. Our results show that the area that was traumatized as a result of the intervention during embryo transfer after hysteroscopy is a favorable environment for implantation and is one of the factors that underpin successful IVF.

Keywords: unicornuate uterus; in vitro fertilization; intracytoplasmic sperm injection; hysteroscopy; implantation failure; infertility

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ART OUTCOMES IN WOMEN WITH ENDOMETRIOSIS AND ADENOMYOSIS

TEVFIK YOLDEMIR, MD, MA, PhD, Prof.

Obstetrics and Gynecology, Marmara University, School of Medicine, Turkey

ABSTRACT

Although endometriosis has been associated with alterations in folliculogenesis, oocyte release from the ovaries, tubal function, and oocyte fertilization, an important point still debated is the effect of the disease on endometrial receptivity and, therefore, on embryo implantation and pregnancy outcomes. It remains to be established if different forms of endometriosis (such as superficial endometriosis or ovarian endometriomas) have a similar impact on the endometrium and whether the presence of adenomyosis affects the endometrium independently or in an additive manner.

Recent teachings suggest that endometriosis itself does not significantly affect success rates, including embryo quality and ploidy, as well as the implantation rate. The outcomes of IVF treatments in patients with endometriosis are comparable to those of control groups, particularly in the context of frozen embryo transfer (FET) conducted during hormonally replaced therapy. Pretreatment hormonal therapies and surgical excision of endometriosis before ET should not be routinely recommended to improve implantation rates. Endometriosis per se does not have a major impact on folliculogenesis. The observed detrimental effect of surgery on the risk of unexpected poor response may reflect an increased difficulty in the oocyte retrieval procedure. Endometriosis is unremarkable to ovarian response. A reduction in the response to ovarian stimulation can be detected only for endometriomas larger than 4 cm. The follicular steroidogenesis is unaffected. Oocyte quality is preserved. Fertilization rate is similar, making ICSI unjustifiable. Embryological development does not differ from other forms of infertility, with no surge in aneuploidy rate. Women with endometriosis, including severe stages and endometriomas, had similar rates of embryo formation, cleavage embryos, and high-quality embryo rates compared with the control group. Endometrial receptivity is not or minimally reduced. To note, the most informative studies supporting this perspective did not exclude women with adenomyosis, a main confounder that was expected to lower the success of the procedure. This further strengthens the idea that women with endometriosis should not be considered at increased risk of implantation failure.

AMH, antral follicle count, body mass index, and previous ovarian response, if any, should be considered for the stimulation protocol. Hormonal suppression with GnRH agonists before an IVF cycle has no significant differences in terms of the number of oocytes and embryos, as well as clinical results. The pregnancy and live birth rates in patients with endometriosis are similar between GnRH agonists and GnRH antagonist treatment options. The stimulation protocol should be discussed with the patient. Studies comparing progestin primed ovarian stimulation (PPOS) vs. GnRH antagonist protocols reported similar number of retrieved oocytes in both study groups, concluding that the PPOS protocol could be a good alternative in women with endometriosis when a fresh embryo transfer is not planned.

Oocyte vitrification offers women with ovarian endometriomas an effective and reliable option to increase their chances of motherhood, mainly when they are young and have large, bilateral endometriomas requiring surgical intervention. Since women with endometriosis are at risk of having a compromised ovarian reserve due to both pathological and iatrogenic causes, it is necessary to consider fertility preservation as a reproductive treatment option.

Women with adenomyosis had lower LBR, clinical pregnancy rate, and ongoing pregnancy rate (compared to those without adenomyosis, and miscarriage rate was higher in women with adenomyosis. Surgical treatment increases natural conception in women with adenomyosis, although the paucity of data, and conversely, treatment with GnRHa does not increase the IVF outcomes. Women with adenomyosis have decreased IVF clinical outcomes. The major part of the studies has not divided focal and diffuse adenomyosis, and this represents a relevant source of bias. Differences in the participants' age, duration of infertility, type of down-regulation protocol used, number and quality of the transferred embryos, number of IVF cycles performed, and the clinical outcomes are present. Studies conducted with standardized diagnostic criteria for adenomyosis are still needed to determine if the different clinical presentations of such a condition could compromise IVF outcomes.

An ultralong protocol is usually used in patients with adenomyosis and good ovarian function. In fresh ET cycles, the ultralong protocol seemed to improve pregnancy outcomes; however, increased gonadotropin duration and dosage increased the economic burden. In patients with poor ovarian function, an ultralong protocol should be adopted with caution. Long/short/antagonist protocols in fresh ET cycles combined with a flexible FET strategy might be a viable choice for patients with adenomyosis and poor ovarian reserve.

Keywords: assisted reproductive technology (ART); in vitro fertilization (IVF); endometriosis; adenomyosis; endometrial receptivity; fertility preservation

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IMPLEMENTATION OF ARTIFICIAL INTELLIGENCE (AI) IN ASSISTED REPRODUCTIVE TECHNOLOGY

ARIEL HOURVITZ, MD, PhD

*Department of Obstetrics and Gynecology, Tel Aviv Sourasky Medical Center,
Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

In recent years, artificial intelligence (AI) techniques have emerged as objective, standardized methods to improve fertility treatment outcomes, particularly in the laboratory setting and in personalized ovarian stimulation.

In this talk, I will review the latest advances in the field and detail the current literature of clinical nodal points that may be supported by AI models for clinical decision making in ART. These currently include pretreatment counselling, initial dosage, trigger suggestion day, follicular imaging, workload balance, and ovulation prediction and determination. I believe that by leveraging these AI's capabilities in data analysis and pattern recognition, healthcare providers can potentially enhance the success rates of ART treatments while also improving patient satisfaction and operational efficiency within healthcare facilities. Thorough and careful validation, to ensure that these models are reliable, accurate, and aligned with clinical standards before widespread adoption, is crucial for the responsible and safe incorporation of these techniques in clinical practice.

The vision is to have an AI clinic support system that includes all nodal points' decision-making support and workload balance, enabling an optimal and cost-effective workflow while optimizing treatment outcome.

Implementing AI in ART treatments aims not to replace the expertise of medical professionals but to complement their knowledge and experience, serving as a decision support tool. The integration of AI in ART, although in its very early stages, may contribute to more accurate assessments, potentially leading to better treatment outcomes. We believe that the responsible implementation of AI will change the way we practice medicine. As Antonio Di Lova observed, "Machines will not replace physicians, but physicians using AI will soon replace those not using it."

Keywords: IVF, ART, artificial intelligence (AI), machine learning (ML)

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750.000 Patients

More than 750.000 patients
have been tested in 25 years

Cancer Genetics

90+ Hereditary and
somatic cancer tests



CONTRACEPTION IN PATIENTS WITH PSYCHIATRIC DISORDERS

JOHANNES BITZER, *Prof. Gynecologist, Obstetrician,
Sexologist, Basel, Switzerland*

ABSTRACT

Psychiatric disorders, including anxiety disorder, depression, bipolar disorder, post-traumatic Stress disorder, Schizophrenia, Eating Disorder, Disruptive Behavior and Dissocial Disorders, Neurodevelopmental Disorders have an impact on Cognition (Emotional regulation and Behavior (Adherence) of the patients potentially having an impact on effectiveness, health risks, tolerability, and eventual benefits of contraceptive method. At the same time, many patients with psychiatric disorders have high-risk pregnancies with increased risk of premature birth, increased risk of postpartum depression, and increased risk of developmental disorders of the neonate, with negative consequences for cognitive, emotional, and social development.

Practice Guide: Each method should be evaluated regarding the impact on adherence, health risks, tolerability, and possible benefits in the individual patient suffering from a psychiatric disorder. In addition, potential interactions of hormonal methods with therapies have to be taken into consideration.

In the presentation, the advantages and disadvantages of the major contraceptive methods in patients with the most frequent psychiatric disorders are presented.

Keywords: contraception; psychiatric disorders; adherence; hormonal methods; health risks; contraceptive counseling

HOW TO UNDERSTAND THE ADOLESCENT BRAIN

JOHANNES BITZER, *Prof. Gynecologist, Obstetrician,
Sexologist, Basel, Switzerland*

ABSTRACT

Adolescence is a life phase with an increased risk of health problems especially in mental and sexual health.

In this life phase there are typical developmental tasks or aims: Building of one's identity including gender identity, separation from the original family and creating a new social environment, development of cognitive and communication skills, control of behavior and frustration tolerance.

The neurobiological processes underlying the transformation are an activation of the striatum, the nucleus accumbens, and a reduction of activities in the prefrontal cortex activating sensation seeking and impulsivity.

This may contribute to high risk behavior, lack of impulse control, irritability, anxiety and depressed mood, drug abuse etc depending on the social circumstances. Counteracting is the adolescents's enormous capacity to learn and adapt with the growing cognitive functions

How can we as gynecologists assist adolescents in this "journey".

Inform them and empower them regarding the protection, prevention and promotion of their physical, mental and sexual health (contraception, STI prevention, Sexual violence)

Help them coping with stress in this life phase of change and instability to reduce anxiety, depression, addiction.

In addition to these basic medical care adolescents need often psychological support by a health care professional of trust.

Support in their curiosity, their novelty seeking and joy of life.

Support them to find or create the group they want to belong to (friendship, social support)

Counsel them regarding the building of an intimate-sexual relationship.

Keywords: adolescence; adolescent brain; neurobiology; sexual and mental health; risk behavior; gynecological counseling

WHEN PMS AFFECTS THE MIND: SSRIS AS A PATH TO EMOTIONAL STABILITY

EKATERINE TCHANTURIA, MD;¹ KETEVAN SHENGELAIA, MD^{2,3,4}

¹ Reproductive Endocrinologist, Tbilisi, Georgia

² Gagua Clinic, Tbilisi, Georgia

³ Ken Walker Clinic, Invited Lecturer, Tbilisi, Georgia

⁴ Med Diagnostics, Tbilisi, Georgia

ABSTRACT

Background: Premenstrual Syndrome (PMS) is a recurrent, hormone-related condition that affects women during the luteal phase of the menstrual cycle. It is characterized by physical, emotional, and behavioral symptoms that typically resolve with the onset of menstruation. While mild premenstrual symptoms are common, approximately 20-40% of women experience symptoms severe enough to impair daily functioning.

At its most severe, PMS manifests as Premenstrual Dysphoric Disorder (PMDD), a clinical diagnosis recognized by the DSM-5 and the American Psychiatric Association. PMDD is primarily marked by mood-related symptoms – such as irritability, anger, emotional instability, anxiety, and depression – often accompanied by physical complaints like breast tenderness, bloating, and headaches.

Objective: To evaluate the role of SSRIs in stabilizing mood and reducing emotional symptoms in women with PMS and PMDD.

Materials and Methods: A structured literature review was performed using PubMed, Cochrane Library, and PsycINFO to identify studies on SSRI use in PMDD. Keywords included “PMDD”, “SSRIs”, “fluoxetine”, “sertraline”, and “premenstrual mood symptoms.” Eligible sources were randomized controlled trials (RCTs), meta-analyses, and clinical guidelines published between 2000 and 2025. Both continuous and luteal-phase dosing regimens were analyzed. Comparative studies involving CBT were also reviewed.

Results: SSRIs, including fluoxetine, sertraline, and paroxetine, demonstrated significant efficacy in reducing core PMDD symptoms, particularly mood swings, irritability, and anxiety. Continuous dosing showed greater symptom control compared to luteal-phase or symptom-onset regimens. SSRIs were generally well tolerated at low doses. CBT provided functional benefits but offered slower symptom relief than pharmacological treatment.

Conclusion: SSRIs are an effective first-line treatment for managing the mood and emotional symptoms of PMDD. Continuous dosing provides the most significant symptom relief, though luteal-phase and symptom-onset regimens remain viable alternatives. While CBT contributes to functional improvement, SSRIs deliver faster symptom control. Early diagnosis and individualized treatment strategies are essential for improving quality of life and emotional stability in women affected by PMDD.

Keywords: premenstrual dysphoric disorder (PMDD); premenstrual syndrome (PMS); selective serotonin reuptake inhibitors (SSRIs); mood disorders; pharmacotherapy; cognitive behavioral therapy (CBT)

NUTRITION, REPRODUCTION, AND AGE

MARI MALAZONIA, MD, PhD^{1,2,3}

¹ David Tvildiani Medical University, Tbilisi, Georgia

² Georgian American University, Tbilisi, Georgia

³ National Nutritional Centre, Tbilisi, Georgia

ABSTRACT

All living things share life processes such as movement, respiration, and growth, among others. Nutrition and reproduction are key characteristics that determine life. At the same time, both are essential for the continuation of human existence.

“Reproductive nutrition” refers to the interrelationship of vital processes. Nutrition affects factors important for reproduction: the human genome, transcriptome, proteome, and metabolome – and, as a result, the individual phenotype and function. According to evidence-based medicine, nutritional status influences reproductive ability. Moreover, a personalized nutritional strategy is necessary to address specific reproductive needs.

There are general nutritional principles for the fertility diet: choose “good” carbohydrates, including whole grains and vegetables; eliminate trans fats and prioritize high-quality fats such as omega-3 fatty acids; increase plant protein intake; replace sugar-sweetened beverages with water or the occasional glass of whole milk; and, if necessary, take a multivitamin containing pro-fertility ingredients.

Age is an individual characteristic that should always be considered in relation to reproductive ability. At the same time, age-specific nutritional needs, energy expenditure, and macro- and micronutrient intake and absorption alter nutritional status.

Overnutrition and undernutrition are risk factors across all age groups. Both obesity and underweight represent forms of malnutrition and place a burden on the reproductive system. In addition, specific nutritional deficiencies at both early and late ages pose risks for reproduction.

In relation to age, processes such as inflammation, glycation, and oxidation must be considered, since all of these affect reproduction. Therefore, it is essential to consume anti-inflammatory foods, antioxidant-rich foods, and functional foods for reproductive health.

Nutrition for reproduction in different age groups is a serious challenge for modern medicine.

To address this challenge, clinicians must consider genetics, lifestyle factors, physical and psycho-emotional health, socioeconomic status, and ethnocultural characteristics. When selecting a nutritional model to address reproductive challenges in different age groups, professionals should also consider individual eating habits and behaviors.

Keywords: reproductive nutrition; nutritional status; fertility diet; malnutrition; age-specific nutrition

REPRODUCTIVE HEALTH CHARACTERISTICS OF ADOLESCENT GIRLS IN GEORGIA

MAKA JORBENADZE, MD, PhD;^{1,2} MARIAM CHIPASHVILI, MD, PhD;^{1,2}

SOPHIO KVALIASHVILI, MD, PhD;¹ JENARO KRISTESASHVILI, MD, PhD;² NINO KURASHVILI, MD^{1,2}

¹ Zhordania Medical Center, Tbilisi, Georgia

² Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: The formation of reproductive function is a long and complex process, which is greatly influenced by genetic, biological, social, economic, ethnic, and religious factors. The period of formation of reproductive function, or puberty, is a transitional period from a sexually immature child to a sexually mature adolescent, which is controlled by complex neuro-endocrine factors, leading to physical and mental changes that result in physical, mental, and reproductive maturation of the organism. Therefore, the completeness with which puberty proceeds and ends is of great importance for the final state of reproductive function, fertility, and prognosis in adolescent girls. One important factor during this period is menarche and the timing of its onset, which is determined by many factors. Since the reproductive system is formed during adolescence, it is important to detect and treat various disorders characteristic of this period (menstrual cycle disorders, androgenization, premature and delayed sexual development, etc.) at an early stage in order to prevent severe forms of disease. This includes the prevention of infertility during the reproductive period and the improvement of reproductive health in Georgia.

Objective: The aim of the study was to assess the function of the reproductive system in adolescent girls in Georgia and compare the results with studies conducted in previous years.

Methods: A clinical-epidemiological study of 524 adolescent girls aged 10-16 years was conducted in Tbilisi to assess the state of the reproductive system. Analysis of retrospective and prospective data was performed to assess reproductive dysfunction in adolescent girls.

Results: The age of menarche in the investigated girls ranged from 10 to 15 years. The average age of menarche was 12.35 ± 0.05 years, which was 0.05 years less than the data obtained as a result of a similar study conducted in 2006 (12.40 ± 0.05 years) and 0.15 years less than the data obtained as a result of a similar study conducted by the I. Zhordania Scientific Research Institute of Human Reproduction in 1984 (12.50 ± 0.04 years). Among menstrual cycle disorders

ders, the most frequently observed were oligomenorrhea (32.8%) and dysmenorrhea (14.8%), while dysfunctional uterine bleeding (3.02%) and amenorrhea (1.56%) were detected relatively rarely. Among the investigated girls, seborrhea-acne was quite frequent (19.5%) and hirsutism was detected in 2.6%.

Conclusion: Thus, studies have shown that the age of menarche in girls is decreasing in Georgia, as in other countries, and among menstrual cycle disorders, the most frequently observed were oligomenorrhea and dysmenorrhea.

Keywords: adolescent; menarche; menstrual cycle disorders; seborrhea-acne; hirsutism

DETERMINATION OF DEPRESSION LEVEL USING THE BECK DEPRESSION INVENTORY IN WOMEN AFTER MEDICAL ABORTION

AHMAD KARIMOV, MD, PhD; KHAITBOEVA F. A.¹

¹ *Department of Obstetrics and Gynecology in Family Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan*

ABSTRACT

Medical abortion in the second trimester is a significant medical and social issue, particularly among women with a complicated obstetric history. In addition to physical consequences, the procedure can provoke pronounced psycho-emotional disorders, including depression. Assessing the level of depression using standardized tools, such as the Beck Depression Inventory (BDI), facilitates early identification and intervention of psychological disturbances in women who have undergone medical abortion.

To determine the level of depression in women after second-trimester medical abortion using the Beck Depression Inventory and to analyze factors influencing the development of depressive symptoms.

The study was conducted at the Multidisciplinary Clinic of the Tashkent Medical Academy between 2024 and 2025. A total of 30 women aged 21 to 38 years who underwent second-trimester medical abortion participated. The level of depression was assessed using the Beck Depression Inventory at two weeks post-procedure. Additional parameters included age, history of reproductive loss, level of social support, and access to psychological care.

According to the data obtained, 40% (12 out of 30) of the women had mild depression (10-18 points), 43.3% (13 out of 30) had moderate depression (19-29 points), and 16.7% (5 out of 30) had severe depression (≥ 30 points). The participants' ages ranged from 21 to 38 years. The highest level of depression was observed among women aged 30-38 years, with 56.3% showing moderate to severe depression. Women under 25 years old mainly exhibited mild depression (60% of cases). The highest levels of depression were noted among women with recurrent pregnancy loss and limited social support.

Discussion
The analysis of the data indicates that most women who undergo second-trimester medical abortion experience clinically significant depressive symptoms. The most vulnerable group includes patients with prior pregnancy losses and inadequate psychological support.. Further research is necessary to develop effective rehabilitation and psychological support programs for this category of patients.

The assessment of depressive states in women after second-trimester medical abortion using the Beck Depression Inventory demonstrated a high level of depression in the majority of participants. The findings highlight the need for comprehensive psychological rehabilitation programs aimed at improving emotional well-being and preventing long-term depressive disorders.

Keywords: abortion; induced/psychology; depression/diagnosis; depressive disorder/epidemiology; Beck Depression Inventory; second trimester pregnancy; pregnancy loss/psychology; social support; psychological rehabilitation

THE ROLE OF ISCHEMIA IN CERVICAL CARCINOGENESIS

APOLON KARSELADZE

Department of Pathology of the National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia

ABSTRACT

Background: The etiological role of HPV in the development of cervical cancer is well recognized, but many facets of the pathogenesis of this process still need to be clarified.

Purpose: To study the peculiarities of vascularization at the stromal-epithelial interface in epithelial covering of the cervix and its alterations in precancerous lesions.

Materials and methods: Peritumoral tissues of 100 patients with precancerous lesions, incipient cancer of the cervix, and the tissues of 50 healthy persons were studied. Traditional histological as well as immunohistochemical methods have been used.

Results: The study reveals that the occurrence of blood capillaries in surface squamous epithelium of the cervix is an ordinary event, both in healthy persons and in peritumoral regions of the patients with squamous cell carcinoma. Metaplastic squamous epithelium has a markedly reduced vascularization and seems to be more sensitive to carcinogenic stimuli. High-grade dysplastic squamous epithelium and carcinoma in situ do not contain blood vessels.

Conclusion: The redistribution of the vascular network at the epithelial-stromal frontier plays a crucial role in maintaining adequate cell metabolism, including that of the epithelial covering. Impairment of this mechanism most probably promotes precancerous alterations.

Experimental and clinical investigations favor the assumption that stromal cells are deeply influenced by viral carcinogens. HPV may alter proliferative capacities of fibroblasts, for example, and hence inhibit their participation in angiogenesis.

Keywords: ischemia and carcinogenesis; ischemia in the cervical epithelium dysplasia; tumor angiogenesis; HPV and stromal cells

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REPRODUCTIVE HEALTHCARE AT RISK: THE ETHICAL RESPONSE TO ZEALOTRY AND INEQUITY

FRANK A. CHERVENAK, MD; AMOS GRUNEBAUM, MD

ABSTRACT

Access to comprehensive reproductive healthcare – including contraception, abortion, and assisted reproduction – is under global threat from a resurgence of ideological zealotry. This presentation analyzes the ethical obligations of physicians to counteract such threats through a principled and historically informed response. We explore how religious and political extremism – both past and present – have imposed restrictions on reproductive autonomy, often at the expense of patient safety, evidence-based care, and professional integrity. Drawing from the Enlightenment legacy and foundational medical ethics as articulated by Dr. John Gregory, we argue for the reaffirmation of medicine as a public trust grounded in science, compassion, and justice.

Modern zealots weaponize conscience clauses, misinform patients, stigmatize abortion and IVF, and erode access through restrictive laws and financial barriers. These actions disproportionately harm the vulnerable, especially low-income women, adolescents, and racial minorities. The reversal of *Roe v. Wade* in the United States exemplifies the consequences of subordinating human rights to sectarian ideology.

We call for an ethical framework that restores moderation (as Cicero urged) and resists absolutist positions on both sides of the reproductive rights debate. Physicians must balance respect for personal conscience with their duty to ensure timely, non-discriminatory care. Upholding autonomy, beneficence, and justice requires resisting political coercion and affirming patients' rights to make informed decisions.

This talk concludes with a call to global solidarity among health professionals. In an era of rising nationalism and moral panic, the professional community must actively defend reproductive healthcare from ideological capture. Ethical leadership is not optional; it is essential.

Keywords: reproductive healthcare; medical ethics; ideological zealotry; reproductive rights; abortion and assisted reproduction; global health equity

OBSTETRIC VIOLENCE IS A MISNOMER: REFRAMING THE DISCOURSE ON MISTREATMENT IN MATERNITY CARE

FRANK A. CHERVENAK, MD; AMOS GRUNEBAUM, MD

ABSTRACT

The term *obstetric violence*, though increasingly invoked in legislative, media, and activist circles, is both clinically imprecise and ethically problematic. While mistreatment during childbirth is a legitimate and pressing global health concern – affecting 1 in 6 women worldwide and disproportionately impacting women of color in the United States – the rhetorical framing of these events as *violence* implies malicious intent, undermining constructive dialogue and alienating healthcare professionals committed to maternal safety.

This presentation critiques the conceptual inflation of the term *obstetric violence*, tracing its origins from historical misuse to its current application in contexts that often include medically indicated and consented interventions. Drawing on empirical data, including WHO categorizations of mistreatment (e.g., non-consensual care, abandonment, discrimination), the talk delineates the scope of systemic failings without conflating them with criminal or violent acts. Ethical principles of autonomy and beneficence, the role of informed consent, and the impact of under-resourced systems are explored.

Furthermore, the talk examines how linguistic choices influence public trust, professional identity, and policy development. Parallels with other medical fields highlight the inconsistency of labeling necessary procedures as *violent*, while the documented rarity of coerced obstetric interventions in legal databases underscores the need for precision in terminology.

Ultimately, the presentation advocates replacing the term *obstetric violence* with *mistreatment in maternity care*, a more accurate, inclusive, and reform-oriented framework. Recommendations include systemic reforms, enhanced training in respectful care, and culturally competent practice. This reframing fosters accountability without undermining the trust and professionalism essential to improving maternal health outcomes globally.

Keywords: obstetric mistreatment; maternity care; autonomy and beneficence; informed consent; respectful care; maternal health outcomes

ENDOCRINE DISRUPTORS. THE NEED OF COMMON SENSE

CAMIL CASTELO-BRANCO, MD, PhD

Prof. Obstetrics and Gynecology, University of Barcelona, Spain, Senior Consultant in Gynecology and Obstetrics, Hospital Clínic, Barcelona, Spain

ABSTRACT

Background: The term endocrine disruptors (ED) as substances that can interfere with the endocrine system in living beings dates back to the early nineties, but it was already known long before that certain chemicals present in the environment could affect, for the most part, human and animal life and health. This includes many diseases throughout the life cycle, such as cancer, genetic modification, metabolic diseases, malfunctioning of various organs, and last but not least, reproduction.

Objective: As for its effect on reproduction and, more broadly, on the endocrine system, it is not surprising that a large part of this issue relates to steroids. In this review we analyze the mechanisms of action and the effects of ED on health.

Material and Methods: Research Databases including CINAHL Plus, Health Source: Nursing Edition, MEDLINE, PsycINFO, Google scholars and Women's Studies International were searched for journal articles on ED published in the past 10 years.

Results: DEs interfere with the biosynthesis and metabolism of steroids, either as inhibitors of the relevant enzymes or at the level of their expression. Particular attention has been devoted to enzymes that metabolize hormonal precursors to biologically active products in their target cells, such as aromatase, 5 α -reductase, and 3 β -, 11 β - and 17 β -hydroxysteroid dehydrogenases. An important target for ED is also the steroid acute regulatory protein (StAR), responsible for the trafficking of steroid precursors to the mitochondria. DEs influence receptor-mediated steroid actions at both genomic and non-genomic levels. The remarkable differences in response to various steroid receptor ligands have originated detailed data from the events following the binding of steroids/disruptors to the receptors and the mapping of the signaling cascades and nuclear factors involved. So far, little information is available on the effects of EDs on the major hypothalamic-pituitary-adrenal/gonadal axes, of which the kisspeptin/GPR54 system is of particular importance. Kisspeptins act as stimulators of GnRH secretion and their expression is regulated by sex steroids through a feedback mechanism. Kisspeptins are now thought to be

one of the key factors that trigger puberty in mammals, and several EDs affect their expression and function. Finally, although advances in the analysis of EDs are becoming more and more noticeable, especially those that persist in the environment, in various body fluids (plasma, urine, seminal fluid and follicular fluid), it is surprising that very little information is available on the simultaneous determination of ED and steroids in the same biological material.

Conclusion: ED has health and social implications that are complex and influenced by multiple factors. Further research is needed to expand and elucidate theoretical relationships between the early development of gynecological and endocrine diseases in women and the proposed causative factors.

Keywords: endocrine disruptors (ED); steroids; steroidogenic enzymes; receptor-mediated actions; kisspeptin/GPR54 system; reproductive health

STEM CELLS IN OBSTETRICS AND PRENATAL MEDICINE

WOLFGANG HOLZGREVE, MD, PhD

*Prof., Head of the Healthcare Management Programme, HBM Entrepreneurs School,
Gallen, Switzerland*

ABSTRACT

Cord blood is successfully used since over 10 years as source of transplantation of hematopoietic stem cells. Allogeneic transplantations are performed between HLA-identical siblings and from HLA-matched unrelated donors. Most recipients of cord blood are children with leukemia or genetic disorders. Based on the promising results, cord blood banks with cryopreserved cord blood samples from anonymous donors are set up worldwide, ready to be used as an allogeneic stem cell graft. Additionally, so-called “private” cord blood banks were set up, providing the possibility to store cord blood at birth from healthy children with no affected family member for a possible autologous stem cell transplantation in the future. The plasticity and multipotency of adult stem cells and the use of induced pluripotent stem cells (iPS-cells) have stimulated not only basic research but also clinical trials for different indications in regenerative medicine (cell- and organ replacement/regeneration).

Prenatal in-utero stem cell transplantation is a promising therapeutic option for genetic disorders, which is now at the edge of moving from preclinical research into clinical application. The first clinical experience shows that some form of severe immunodeficiency can be treated successfully in utero. No therapeutic success has been achieved in genetic disorders that do not severely affect the immune system. Therefore, new strategies are being developed, including graft modification, prenatal conditioning of the fetus, postnatal re-transplantation after prenatal induction of immune tolerance, and fetal gene therapy using autologous fetal stem cells. The use of non-hematopoietic (e.g., mesenchymal) or pluripotent stem cells will probably lead to an expansion of the spectrum of indications.

Keywords: stem cells; cord blood transplantation; prenatal therapy; induced pluripotent stem cells (iPS cells); regenerative medicine; in-utero stem cell transplantation



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UPDATE ON NON-INVASIVE PRENATAL TESTING. HOW DID NIPT CHANGE THE PRACTICE OF PRENATAL DIAGNOSIS?

WOLFGANG HOLZGREVE

Dr. med., Dr. h.c. mult., MBA, MS, FACOG, FAGOS, FRCOG

ABSTRACT

Objective: Despite progress in invasive prenatal procedures a burden always was the risk of, therefore the search for a non-invasive test (NIPT), which became successful by looking at cell-free DNA (NIPT) in the maternal blood (1) So far, however, real world data were missing how the shift from amniocentesis to NIPT really evolved and what the actual numbers of the changes are.

Methods: In order to obtain this important information, a multicentre study of different Prenatal Medicine Centers, including our University Medical Center in Bonn, was conducted in Germany (3) and followed up by the most recent data (so far unpublished).

Results: It was found that from 2003 to 2020, the number of amniocentesis has decreased from 54393 to 7182, whereas the CVS number has stayed constant between 4200 and 4500, and this trend continued into 2025, which means a reduction of AC and CVS per birth from 8.3 to 1.5% up to this year.

Conclusion: We can now, for the first time, present the most recent data on NIPT and calculate how many fetal losses caused by invasive procedures were saved by NIPT. It is not common in medicine for the introduction of a new technological offer to women to significantly alter practice, thereby reducing major risks and raising ethical implications.

Keywords: non-invasive prenatal testing (NIPT); cell-free DNA; amniocentesis; chorionic villus sampling (CVS); prenatal diagnosis; fetal loss reduction

INFERTILITY AFTER 40: A CHALLENGE FOR MODERN REPRODUCTIVE MEDICINE

VYACHESLAV LOKSHIN, PhD

*Kazakhstan Association of Reproductive Medicine, International Center
for Clinical Reproductology PERSONA, Almaty, Kazakhstan*

ABSTRACT

Modern reproductive medicine faces a growing trend of postponing the birth of a first child to a later age. Socioeconomic and cultural changes contribute to the increasing age of women seeking infertility treatment. However, physiological limitations and declining fertility after the age of 40 present a significant challenge for assisted reproductive technology (ART) specialists. The effectiveness of infertility treatment for women over 40 does not exceed 5-15%, similar to the probability of natural conception. While women under 40 have a 25-30% chance of conceiving per cycle, this probability drops to 12-15% at ages 40-42 and to less than 5% after 43. The use of donor oocytes increases the chances of pregnancy to 50-60%.

Infertility after 40 remains a serious challenge for modern reproductive medicine. Despite the declining effectiveness of traditional methods, new technologies and personalized approaches offer promising opportunities for successful conception and pregnancy. However, age-related limitations necessitate a balanced approach that includes not only medical but also psychological, ethical, and social considerations. The issue of late motherhood requires continued scientific research and the development of educational programs to inform women about reproductive health and timely family planning.

Keywords: infertility; assisted reproductive technology; oocyte quality; preimplantation genetic testing; advanced maternal age; oocyte cryopreservation

UNSOLVED ISSUES OF MODERN REPRODUCTIVE MEDICINE

VYACHESLAV LOKSHIN, PhD

*Kazakhstan Association of Reproductive Medicine, International Center
for Clinical Reproductology PERSONA, Almaty, Kazakhstan*

ABSTRACT

Despite significant progress in assisted reproductive technologies (ART), a number of fundamental challenges remain unresolved. Modern reproductive medicine is confronted with new and complex issues – from age-related fertility decline to the problem of endometrial receptivity, male infertility, and pressing ethical and social concerns.

Key Unresolved Issues:

1. Age-Related Decline in Female Fertility:

- After age 35, there is a sharp decline in ovarian reserve and oocyte quality
- ART success rates in women over 43 remain critically low
- Ongoing debate over age limits and access to donor oocytes in ART programs

2. Implantation Failure and Endometrial Receptivity:

- Up to 70% of IVF failures are linked to impaired endometrial receptivity
- Lack of reliable clinical methods for diagnosing the “implantation window”
- The roles of immune system and uterine microbiome remain poorly understood

3. Embryo Quality and Selection:

- High rates of aneuploidy, especially in advanced maternal age
- Limited predictive value of traditional morphological embryo assessment
- Limitations of preimplantation genetic testing (PGT-A); need for non-invasive methods and AI-based embryo evaluation

4. Male Factor Infertility:

- Increasing incidence of idiopathic oligo- and asthenozoospermia
- Limited effectiveness of current treatments for spermatogenesis disorders
- Need for molecular diagnostics and personalized therapies

5. Ethical and Social Challenges:

- Inequitable access to ART across different socio-economic groups
- Ethical debates surrounding surrogacy, embryo editing, and gamete donation
- Insufficient reproductive education and awareness, especially among young people

Conclusion: Modern reproductive medicine must address a wide spectrum of unresolved biological, technological, and ethical challenges. Continued fundamental research, the implementation of personalized and multidisciplinary approaches, as well as government support and early fertility education programs are essential for the future of reproductive healthcare.

Keywords: assisted reproductive technologies (ART); female fertility decline; endometrial receptivity; embryo selection; male infertility; ethical challenges in reproduction

SPERM DNA FRAGMENTATION IN MALE PARTNERS OF COUPLES WITH UNEXPLAINED INFERTILITY AND RECURRENT PREGNANCY LOSS IN GEORGIA

TEIMURAZ GAGNIDZE, MD, PhD

General Director, Center for Reproductive Medicine "Universe", Tbilisi, Georgia;

President, Association of Andrologists of Georgia, Tbilisi, Georgia

ABSTRACT

Infertility has become a widespread global health issue, impacting approximately 15% of couples worldwide, with male factors responsible for 50% of all infertility cases. Conventional semen analysis (SA) is the standard method for evaluating male fertility, but it is a limited predictor of reproductive outcomes. Extensive research on sperm-testing methods has identified sperm DNA damage as a crucial factor in the pathophysiology of male infertility. According to literature data, sperm DNA fragmentation (SDF) can't be considered an essential cause of recurrent pregnancy loss (PRL)

Objective: Detection of SDF degree in male partners of couples with unexplained infertility and RPL, and revealing the correlation between SDF and semen parameters

Patients and Methods: 167 couples (aged 24-44 years) were investigated at CRM "Universe" (Tbilisi, Georgia) in 2017-24. I group – 88 couples with ≥ 2 unexplained miscarriages, II group – 79 couples with primary unexplained infertility, III group – control (42 sperm donors). Common causes of RPL and infertility were excluded for all couples. In all men, the SDF degree was assessed by the SCD method.

Results: Mean SDF index (SDFI) in I ($32,8 \pm 10,8$) and II ($29,1 \pm 10,3$) groups didn't differ significantly but were substantially higher compared to the control group ($13,9 \pm 3,1$). SDFI more than 15% was considerably higher than SDFI less than 15% in I and II groups, whereas in the III group, the opposite was observed. In the RPL group, SDFI positively correlates ($r=0.39$, $P<0.01$) with the number of recurrent miscarriages and sperm abnormal forms and negatively correlates with sperm motility and concentration. In the Infertility group, SDFI positively correlated with sperm abnormal forms and negatively correlated with sperm volume, total sperm count, and progressive motility.

Conclusions: Evaluation of sperm DNA damage is a more reliable independent predictor of male fertility compared to traditional semen analysis. Assessment of SDFI is recommended in male partners of couples with unexplained infertility and RPL. For SDFI normalization, elaboration of possible treatment (correction of varicocele, obesity, avoidance of smoking and alcohol consumption, treatment of STD) and preventive measures might be used for preconception preparation of men, with antioxidants, especially with folates.

Keywords: infertility; pregnancy loss; sperm DNA fragmentation

MICRO-TESE: THE LEADING SURGICAL SOLUTION FOR SEVERE NON-OBSTRUCTIVE AZOOSPERMIA

**BEKA SIBASHVILI, MD; SHALVA CHOVELIDZE, MD; TENGIZ ZHORZHOLADZE, MD;
NINO KUTCHUKHIDZE, MD; EKATERINA VOLKOMOROVA, MD; LIA CHKONIA, MD**
Georgian-American Center for Reproductive Medicine (ReproART), Tbilisi, Georgia

ABSTRACT

Background: Non-obstructive azoospermia (NOA) represents one of the most challenging conditions in male infertility, often resulting from severely diminished or absent sperm production. Traditional methods for sperm retrieval are frequently unsuccessful in these patients. Microdissection testicular sperm extraction (micro-TESE) is an advanced surgical technique that offers higher retrieval rates while minimizing damage to testicular tissue.

Objective: To evaluate the effectiveness and safety of micro-TESE in men with severe NOA and to assess how patient selection, histopathologic findings, and hormonal management influence procedural success.

Materials and Methods: A retrospective analysis was conducted on 27 men with NOA who underwent micro-TESE at the Georgian-American Center for Reproductive Medicine (ReproART) between 2023 and 2025. Preoperative evaluation included serum hormone levels (FSH, LH, testosterone, prolactin, E2), genetic testing, and testicular volume measurement. High-magnification microscopy (×20-25) was used intraoperatively to identify seminiferous tubules most likely to contain active spermatogenesis. Surgical findings and histopathology were compared with sperm retrieval outcomes.

Results: Sperm retrieval was successful in 62.9% of patients. Retrieval depended primarily on detecting even a small focus of spermatogenesis; thus, testicular volume, FSH levels, and coexisting male health conditions were not reliable predictors of outcome. Micro-TESE achieved higher retrieval rates than conventional TESE, particularly in men with Sertoli cell-only syndrome or maturation arrest. No significant long-term postoperative complications or hypogonadism were observed.

Conclusions: Micro-TESE is the most effective and safest method for sperm retrieval in severe NOA. Optimal outcomes depend on careful patient selection, hormonal optimization, and surgical expertise. Recognized as the current gold standard, micro-TESE provides hope for biological parenthood in the most challenging cases of male infertility.

Keywords: micro-TESE; non-obstructive azoospermia; male infertility; sperm retrieval; testicular histopathology

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COMPARISON OF TWO SPERM PROCESSING METHODS AND THEIR IMPACT ON FERTILIZATION, EMBRYOGENESIS, AND EUPLOIDY RATES

**TEMIKO ZHORZHOLADZE; NINO KUTCHUKHIDZE; EKATERINA VOLKOMOROVA;
BEKA SIBASHVILI; MARIAM SHERVASHIDZE; THEA PATARAIA; TAMAR BARBAKADZE;
TAMAR KBILASHVILI; MARIAM GABADZE; LIA CHKONIA**

Georgian-American Center for Reproductive Medicine REPROART, Tbilisi, Georgia

ABSTRACT

Background: Optimizing sperm selection techniques is essential (changed from *crucial*) for improving fertilization, embryo development, and genetic competence in assisted reproductive technology (ART). Two widely used sperm preparation methods – density gradient centrifugation (DGC) (changed from *Density Gradient Centrifugation*) and microfluidic sperm sorting (ZyMöt) (changed from *Microfluidic Sperm Sorting (ZyMöt)*) differ in their ability to isolate motile, morphologically normal spermatozoa. Their comparative clinical performance remains under evaluation (changed from *a topic of interest*).

Objective: To compare IVF outcomes (changed from *the outcomes of IVF cycles*) using ZyMöt versus DGC sperm preparation, focusing on fertilization (2PN rate), blastocyst development (changed from *blastocyst formation*), and euploidy rates.

Materials and Methods: A retrospective review of 60 ICSI cycles conducted at Reproart between January and August 2025 (changed from *conducted between January and August 2025 at Reproart*) was performed. The study involved couples where the female partner was aged <40 years (changed from *under 40 years old*) and the male partner had a sperm count of ≥ 1 million/mL with at least 5% progressive motility. Sperm samples with DNA fragmentation >50% were excluded. Only mature (MII) oocytes were used (changed from *All oocytes used were MII*). Patients were divided into two equal groups:

- Group 1 (ZyMöt): 30 cycles, 240 MII oocytes, 218 2PN, 126 blastocysts, 67 euploid embryos.
- Group 2 (DGC): 30 cycles, 257 MII oocytes, 221 2PN, 112 blastocysts, 54 euploid embryos.

Results: The ZyMöt group demonstrated higher 2PN fertilization (90.8% vs. 85.9%), blastocyst formation rate from 2PN embryos (changed from *blastocyst formation*) (57.8% vs. 50.7%), and euploidy rate per blastocyst (changed from *euploidy rates per blastocyst*) (53.1% vs. 48.2%) compared to DGC. Statistical significance is under evaluation (changed from *under evaluation*).

Conclusions: Microfluidic sperm preparation with ZyMöt shows a trend toward improved outcomes in ICSI cycles compared with conventional DGC. Pending statistical confirmation, these findings suggest that microfluidic selection may enhance ART success rates. (Changed from *If statistically confirmed. These findings may support wider adoption of microfluidic selection to enhance ART success rates.*)

Keywords: ZyMöt; density gradient centrifugation; ICSI; euploidy; blastocyst (formatted to conference book style, changed from *ZyMot; Density Gradient Centrifugation; ICSI; Euploidy; Blastocyst*)

FERTILITY PRESERVATION: CURRENT TRENDS, CHALLENGES, AND OPPORTUNITIES

LUDMILA BARBAKADZE, MD, PhD;¹ NATALIA KHONELIDZE, MD, PhD;²

GIA TSAGAREISHVILI, MD, PhD²

¹ Assistant Professor, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia² Clinical Professor, Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Fertility preservation (FP) has become a key aspect of reproductive medicine, initially developed for patients undergoing gonadotoxic cancer treatments. With advances in healthcare and changing social trends, FP now serves a broader population, including pediatric, adolescent, and transgender individuals, as well as those electing to delay childbearing for non-medical reasons.

This review provides a comprehensive and evidence-based synthesis of the current state of fertility preservation, emphasizing both medical and elective indications. The goal is to highlight recent advances, ongoing challenges, and emerging opportunities to guide clinical practice and healthcare policy, supporting informed decision-making and equitable care globally.

Medical indications for FP encompass patients undergoing gonadotoxic therapies for cancer, as well as individuals with genetic or autoimmune disorders requiring cytotoxic therapies, and other conditions compromising reproductive potential. Established FP methods include embryo, oocyte, and sperm cryopreservation, as well as ovarian or testicular tissue preservation. Ovarian tissue cryopreservation is particularly indicated in pediatric or urgent scenarios in which ovarian stimulation is not feasible. Multidisciplinary care frameworks are pivotal for timely referral, individualized counseling, and optimized treatment outcomes.

Elective FP reflects sociocultural shifts, with many individuals – predominantly women – choosing to postpone parenthood for educational, professional, or personal reasons. Elective oocyte cryopreservation allows preservation of fertility potential before age-related decline, supported by improved vitrification techniques. Collaboration across oncology, reproductive medicine, psychology, and policy sectors is paramount to enhance equitable and effective fertility preservation worldwide.

In conclusion, fertility preservation is a rapidly advancing field at the intersection of clinical care and reproductive choice. While significant progress has been made in technology and access, ongoing challenges – such as ethical concerns, disparities, and experimental methods – require continued multidisciplinary collaboration. Ensuring equitable, informed, and patient-centered care is essential to optimizing reproductive outcomes worldwide.

Keywords: fertility preservation; reproductive medicine; delayed childbearing; cancer treatment



ნეიროგენეტიკისა და მეტაბოლიზმის ცენტრი N G M C

ნეიროგენეტიკისა და მეტაბოლიზმის ცენტრი 2017 წლიდან ასრულებს
შუამავალი ლაბორატორიის ფუნქციას ქართველ პაციენტებსა და
სხვადასხვა ქვეყნის წამყვან ლაბორატორიებს შორის.

ჩვენ უზრუნველვყოფთ დროულ, ხარისხიან და ხელმისაწვდომ სერვისებს.
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სერვისები

გენეტიკა:

- სრული ეგზომის სექვენირება (Whole Exome Sequencing)
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აუტიზმი

- მყიფე X სინდრომი
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- სპინალური კუნთთა ატროფიის მტარებლობა

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ალ ყაზბეგის გამზ 14ბ
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OUR DUTY IS TO
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FERTILITY PRESERVATION IN WOMEN WITH TURNER SYNDROME

YOSSI MIZRACHI, MD

*Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Director, Fertility Unit,
Edith Wolfson Medical Center, Holon, Israel*

ABSTRACT

Turner Syndrome is characterized by accelerated oocyte apoptosis during fetal life, resulting in severely diminished ovarian reserve from birth. Consequently, only 15-20% of affected individuals undergo spontaneous puberty, with clinical severity correlating with karyotype, being most pronounced in those with 45X monosomy and more variable in cases of mosaicism. The vast majority ultimately develop premature ovarian insufficiency (POI). Many patients and their families seek fertility preservation (FP) counselling at a young age. Oocyte cryopreservation is currently the most established FP method, feasible in individuals who experience spontaneous puberty. Both genotype and serum AMH levels are useful predictors of potential success. In contrast, ovarian tissue cryopreservation (OTC) in prepubertal girls with Turner Syndrome has demonstrated limited efficacy, with inferior outcomes to date. Recently, two novel and thought-provoking approaches have been reported: (1) ovarian stimulation in prepubertal girls with Turner Syndrome, and (2) ovarian tissue transplantation from an HLA-compatible, non-affected sister. While these strategies remain experimental, they open potential avenues for future research and clinical innovation. Despite these developments, FP in Turner Syndrome remains highly challenging, and realistic, evidence-based counselling is essential.

Keywords: turner syndrome; fertility preservation; premature ovarian insufficiency (POI); oocyte cryopreservation; ovarian tissue cryopreservation (OTC); anti-Müllerian hormone (AMH)

"OOCYTE CRYOPRESERVATION AS A LIFE STRATEGY: CLINICAL OUTCOMES AND PATIENT EMOTIONS"

SHOLPAN KARIBAYEVA, MD

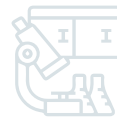
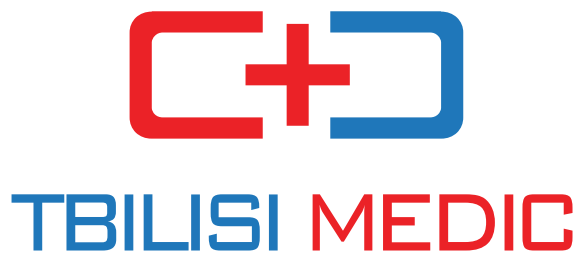
Department of Obstetrics and Gynecology, MCCR Persona, Almaty, Kazakhstan

ABSTRACT

Modern socio-economic realities have dramatically reshaped reproductive behavior across the globe. Increasingly, women are choosing to delay motherhood in pursuit of personal growth, career development, education, and emotional maturity. Although these social changes are positive, they conflict with biological constraints, as female fertility declines markedly after 35 years of age and even more sharply after 40 years.

Social oocyte cryopreservation (SOC) is a proactive strategy that enables women to preserve reproductive potential by freezing oocytes at a younger age for possible future use. Beyond its clinical application, SOC has evolved into a meaningful life strategy, supporting reproductive autonomy, psychological reassurance, and a sense of control over fertility planning. Even when clinical outcomes are uncertain, many women report reduced anxiety and increased confidence in their reproductive choices. Continued progress requires refinement of clinical protocols and age-specific guidelines, integration of psychological support into fertility preservation counseling, and promotion of accurate, ethical, and culturally sensitive education. While SOC does not guarantee motherhood, it represents a declaration of intent, autonomy, and hope. The role of reproductive professionals is to guide this choice with honesty, evidence, and compassion.

Keywords: oocyte cryopreservation; fertility preservation; reproductive autonomy; patient counseling; psychological well-being; ethical considerations



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THE LATEST STANDARDS OF MODERN DIAGNOSTICS AND CLINICAL PRACTICE OF UTERINE PATHOLOGIES

GEORGE TEVDORASHVILI, MD, PhD

Tbilisi State Medical University, The First University Clinic, Tbilisi, Georgia

ABSTRACT

Background: The endometrium, the inner lining of the uterine cavity that directly participates in the menstrual cycle and embryo implantation processes, is one of the leading indicators of gynecological and reproductive health. It responds cyclically to hormonal changes regulated by the hypothalamic-pituitary-ovarian axis (HPO) and undergoes morphological transformations during all phases of the menstrual cycle. Dysfunctional endometrium is defined as a disruption or impairment of the endometrial response to normal hormonal stimulation. Dysfunctional endometrium often underlies the development of abnormal uterine bleeding (AUB) and other pathological processes and requires in-depth evaluation. Ultrasound examination is an essential stage of gynecological diagnostics. Transvaginal sonography and sonohysterography (SIS) are methods instrumental in detecting structural gynecological pathologies of the endometrial cavity, establishing differential diagnosis, and planning proper management.

Objective: To review the anatomical and functional features and hormonal regulation of the endometrium, emphasize the importance of ultrasound assessment, present the latest classification systems for the main endometrial pathologies (endometrial polyps, endometrial hyperplasia and malignancy, uterine leiomyoma, adenomyosis, post-cesarean section scar defect – isthmocele), analyze modern diagnostic methods, and provide recommendations based on the latest evidence for the management of structural gynecological pathologies.

Methods: The review is based on the latest scientific literature, guidelines, classification systems, practice bulletins, and consensus statements from leading organizations (FIGO, ACOG, WHO), as well as clinical experience from leading experts in the field. Special emphasis is placed on the role of ultrasound methods, including sonohysterography (SIS), especially in cases where standard visualization of the endometrium is limited.

Results: Endometrial assessment using the latest ultrasound techniques, with proper interpretation, significantly increases the rate of identification of the causes of AUB and ensures timely diagnosis of endometrial pathologies, providing an important basis for successful treatment.

Sonohysterography (SIS) significantly improves detection of structural pathologies of the endometrial cavity and reduces the number of unnecessary invasive interventions.

Conclusions: Hormonal and structural assessment of the endometrium remains a central component of modern gynecology. An integrated, individualized approach – combining clinical, ultrasound, and histological data – leads to accurate diagnosis and effective treatment planning, representing an essential prerequisite for targeted personalized management and improved patient well-being.

Keywords: endometrium; hormonal regulation; endometrial pathologies; SIS; sonohysterography; transvaginal ultrasound; AUB; endometrial polyps; endometrial hyperplasia; endometrial cancer; leiomyoma; adenomyosis; isthmocele

COMPARATIVE EFFECTIVENESS OF SHORT-COURSE ORAL METRONIDAZOLE FOR BACTERIAL VAGINOSIS IN REPRODUCTIVE-AGE WOMEN WITH VITAMIN D DEFICIENCY: WITH AND WITHOUT VITAMIN D THERAPY

MARIAM TEVDORASHVILI;¹ DAVID TEVDORASHVILI;¹ GEORGE TEVDORASHVILI;²
NATO METSKHVARISHVILI²

¹ Medical Center "Laser"

² Tbilisi State Medical University (TSMU), Tbilisi, Georgia

ABSTRACT

Background: Bacterial vaginosis (BV) is a common condition in women of reproductive age, with a prevalence of 22.3% in Georgia (changed from *accounting for 22.3% in our region, Georgia*). BV can lead to various complications, while vitamin D deficiency – affecting approximately 37% of the Georgian population (changed from *affecting 37%*) – has also been linked to a higher risk of BV.

Objective: To evaluate the effectiveness of short-course oral metronidazole for symptomatic BV in women with vitamin D deficiency, comparing outcomes between those receiving concurrent vitamin D therapy (changed from *treated with vitamin D*) and those who did not.

Materials and Methods: A total of 33 non-pregnant, non-smoking women (mean age 25 ± 5 years) with symptomatic BV and vitamin D deficiency were enrolled. Diagnosis of BV was confirmed using Nugent scoring, Amsel criteria, and culture. Participants were randomized into two groups:

- Study group (n=21): vitamin D therapy weekly for 105 ± 10 days plus oral metronidazole 500 mg twice daily for 5 days.
- Control group (n=12): oral metronidazole only, without vitamin D.

Clinical and laboratory assessments were performed on days 5, 7, 14, and 28.

Results: In the study group, 17 women (80.9%) achieved recovery by day 5 (normal vaginal discharge 1-4 ml, pH 4.0-4.5, Nugent 0-3). Four women (19.1%) required extended treatment to 7 days. In the control group, only 3 women (25%) recovered by day 5, while 9 (75%) required 7 days of therapy. Follow-up on days 14 and 28 showed no recurrence in the study group.

Conclusions: Short-course metronidazole (500 mg twice daily for 5 days) was significantly more effective when combined with vitamin D therapy than when used alone. The combined approach led to faster recovery, reduced recurrence, and clinical as well as pharmacoeconomic benefits.

Keywords: bacterial vaginosis; vitamin D deficiency; vitamin D therapy; short-course metronidazole; Nugent score; Amsel criteria; recurrence prevention

LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE (LNG-IUD) IN WOMEN WITH UTERINE FIBROIDS: A SAFE AND EFFECTIVE OPTION FOR BLEEDING CONTROL AND CONTRACEPTION

**MARIAM TEVDORASHVILI;¹ DAVID TEVDORASHVILI;¹
GEORGE TEVDORASHVILI;² NATO METSKHVARISHVILI;²
MARIAM NEMSITSVERIDZE;³ TATA SKHIRTADZE⁴**

¹ Medical Center "Laser", Tbilisi, Georgia

² Tbilisi State Medical University, Tbilisi, Georgia

³ Gagua Clinic, Tbilisi, Georgia

⁴ Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Background: Uterine fibroids are benign monoclonal tumors arising from the smooth muscle cells of the myometrium. The incidence of leiomyoma is approximately 20% in women under 30 years and up to 40% in women under 40 years. Symptoms may include menorrhagia, heavy menstrual bleeding, and pelvic pain. The intrauterine device (IUD) is among the most effective contraceptive methods. However, concerns exist that IUD use may worsen uterine bleeding in women with fibroids.

Objective: This study aimed to evaluate the safety and effectiveness of LNG-IUD use among women with uterine fibroids.

Methods: A total of 30 premenopausal women aged 35-50 years were included. All patients met the following criteria: uterine size <12 weeks of gestational age, uterine cavity <10 cm in length, and presence of at least one leiomyoma >2 cm³. Hemoglobin concentration and menstrual blood volume were measured before and after LNG-IUD insertion. The LNG-IUD was inserted within the first 3-5 days of the menstrual cycle. Total uterine and leiomyoma volumes were calculated using the prolate ellipse formula ($a \times b \times c \times 0.523$). Follow-up visits were conducted at 1, 3, 6, and 12 months.

Results: The LNG-IUD was effective in managing menorrhagia associated with leiomyoma. The median pictorial blood loss assessment chart (PBAC) score decreased from 150.0 (range 80.0-250.0) at baseline to 50.0 (0-94.0) at 6 months and 35.0 (0-90.0) at 12 months. Median hemoglobin concentration increased significantly after insertion. No significant changes were observed in uterine or leiomyoma volumes.

Conclusion: The LNG-IUD appears to be a safe and effective contraceptive option for women

with uterine fibroids. It does not adversely affect bleeding caused by leiomyomas, nor does it significantly influence fibroid growth or uterine volume. Its efficacy in reducing menstrual blood loss supports its role as a treatment option for women with fibroids. Further research is required to assess long-term outcomes.

Keywords: levonorgestrel-releasing intrauterine device (LNG-IUD); uterine fibroids; menorrhagia; heavy menstrual bleeding; contraception; hemoglobin level; fibroid volume

ASSESSING CONTRALATERAL TUBAL PATENCY WITH HYSTEROSALPINGOGRAPHY (HSG) IN UNILATERAL TUBECTOMY: A CASE OF PREGNANCY ACHIEVED THROUGH CONTRALATERAL OVULATION

GIORGI TSKRIALASHVILI, *Doctor Reproductologist*

Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Spontaneous conception in patients with unilateral tubectomy is rare, particularly when ovulation occurs on the side without a fallopian tube. This case demonstrates how accurate imaging and individualized management can lead to successful outcomes even in anatomically compromised situations.

Objective: To explore the role of hysterosalpingography (HSG) in fertility planning and to highlight the potential for conception even when ovulation occurs on the side lacking a tube.

Materials and Methods: A 34-year-old woman presented with secondary infertility three years after a left-sided tubectomy for ectopic pregnancy. Hormonal profiling and imaging revealed anovulatory cycles, uterine fibroids, and a functioning right fallopian tube confirmed via HSG. In a stimulated cycle with clomiphene citrate (50 mg twice daily for 5 days), two dominant follicles developed in the left ovary, where the tube was absent. Ovulation was induced with choriogonadotropin alfa (250 mcg).

Results: Despite left-sided ovulation and absence of the ipsilateral tube, intrauterine pregnancy was confirmed through serial hCG measurements and ultrasound. At the time of submission, the pregnancy was ongoing at 19 weeks with normal fetal development.

Conclusions: This case emphasizes the possibility of cross-tubal ovum pick-up, where the contralateral patent tube captures the oocyte from the ovary on the tubeless side. It challenges traditional assumptions about tubal anatomy and fertility. HSG played a central role in assessing tubal status. Clinicians should recognize that successful conception remains possible even when ovulation occurs on the tubeless side.

Keywords: unilateral tubectomy; hysterosalpingography; cross-ovulation; infertility; tubal transport

O-RADS ULTRASOUND ASSESSMENT OF OVARIAN AND ADNEXAL MASSES: DIAGNOSTIC PERFORMANCE AND RISK STRATIFICATION

NATIA MISIRELI, MD;¹ LANA EZIESHVILI, MD;² NATIA PKHALADZE, MD, PhD²

¹ *The First University Clinic, Department of Radiology, Tbilisi, Georgia*

² *The First University Clinic, Department of Obstetrics and Gynecology, Tbilisi, Georgia*

ABSTRACT

Objectives: To provide a comprehensive overview of the ultrasound-based O-RADS (Ovarian-Adnexal Reporting and Data System) used for evaluation and characterization of ovarian and adnexal masses. This study summarizes standardized criteria, imaging features, and risk categories that guide accurate clinical decision-making, minimize unnecessary surgical interventions, and support fertility-preserving strategies whenever feasible.

Materials and Methods: Patients with clinically suspected ovarian or adnexal lesions were referred to the Radiology Department for ultrasonographic evaluation. A transabdominal and/or transvaginal pelvic ultrasound was performed depending on clinical indication. Each lesion was assessed using the O-RADS classification system, considering ultrasound features such as lesion size, internal structure (cystic, solid, or complex), papillary projections, septations (unilocular or multilocular), and vascularity. Based on these features, a risk category (O-RADS 0-5) was assigned. Final classifications were correlated with clinical outcomes, including surgical findings, histopathology, or follow-up imaging, when available.

Results: This prospective observational study included 83 patients with ovarian and adnexal masses. A strong positive correlation was observed between O-RADS categories and final diagnostic outcomes. A p-value <0.001 was derived, indicating a statistically highly significant difference in the distribution of benign and malignant lesions across O-RADS grades. These results support the diagnostic performance of the O-RADS system in stratifying risk and guiding clinical management. Transvaginal ultrasound was superior for initial screening.

Conclusion: The O-RADS ultrasound risk stratification system demonstrated high diagnostic accuracy in differentiating benign from malignant adnexal masses. No malignant lesions were observed in categories O-RADS 1-3, whereas categories 4 and 5 were strongly associated with malignancy. O-RADS 1 and 2 correspond to physiological or benign findings that typically require no intervention. O-RADS 3 represents an indeterminate category requiring expert inter-

pretation. Lesions classified as O-RADS 4 or 5 – characterized by solid components, septations, or irregular margins – require further diagnostic workup and histopathological confirmation.

Keywords: ovarian cancer; O-RADS; transvaginal ultrasound; adnexal masses

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PROGESTERONE-PRIMED STIMULATION VS GnRH ANTAGONISTS: A COMPARATIVE REVIEW

**TAMAR KBILASHVILI, MD;² MARIAM GABADZE;¹ TAMAR BARBAKADZE, MD;²
TEA CHARKVIANI;¹ THEA PATARAIA;¹ MARIAM SHERVASHIDZE;¹ NINO KUTCHUKHIDZE;¹
TEMIKO ZHORZHOLADZE, MD;¹ EKATERINA VOLKOMOROVA;¹ LIA CHKONIA, MD²**

¹ Georgian-American Center for Reproductive Medicine REPROART, Tbilisi, Georgia

² Reproart I Georgian-American Center for Reproductive Medicine

ABSTRACT

Background: Controlled ovarian stimulation (COS) plays a pivotal role in IVF, particularly in egg donor treatment cycles. GnRH antagonist protocols are widely used due to their shorter duration and lower risk of ovarian hyperstimulation syndrome (OHSS). Recently, progestin-primed ovarian stimulation (PPOS) has emerged as a practical alternative, offering protocol simplicity, affordability, and reliable suppression of premature LH surges. Despite growing use, comparative data on PPOS versus GnRH antagonists in egg donors remain limited. This study compares LH dynamics, oocyte yield, fertilization efficiency, and blastocyst outcomes between the two protocols in donor cycles at Reproart.

Objective: To compare the effectiveness of progesterone-primed versus GnRH antagonist protocols for pituitary suppression during COS in oocyte donors, focusing on LH levels, oocyte retrieval, fertilization, and blastocyst formation.

Materials and Methods: A retrospective cohort study was conducted at Reproart, including 80 egg donors who underwent IVF/ICSI between June 1, 2024, and May 31, 2025. Donors were divided into:

- Group A (n = 40): PPOS protocol (oral dydrogesterone 20 mg/day from Day 2)
- Group B (n = 40): GnRH antagonist protocol (Cetrorelix 0.25 mg/day starting when follicles ≥ 13 mm)

All patients received rFSH (150-225 IU/day) from Day 2. Final maturation was triggered with a dual trigger: r-hCG (85 mcg) and Triptorelin (0.2 mg) when ≥ 3 follicles ≥ 17 mm were observed. LH was measured on Days 2, 5, 7, 9, and trigger day. Oocyte retrieval occurred 36 hours later, followed by ICSI. Outcomes included fertilization (Day 1), blastocyst formation (Days 5-7), donor age, total and mature oocytes, and blastocyst quality. Data were extracted from electronic medical records. Ethics approval was obtained.

Results: Trigger-day LH was higher in the PPOS group (5.6 ± 2.4 IU/L) vs. the antagonist group (3.3 ± 1.4 IU/L), though not statistically significant ($p = 0.09$). Oocyte yield: 14.3 ± 3.0 (PPOS) vs. 13.9 ± 3.4 (antagonist), $p = 0.58$. Fertilization rate: 74.0% (PPOS) vs. 75.5% (antagonist), $p = 0.42$. Blastocyst formation rate: 55.0% (PPOS) vs. 58.2% (antagonist), $p = 0.25$. No premature LH surges or cycle cancellations occurred.

Conclusion: PPOS and GnRH antagonist protocols demonstrated comparable effectiveness in pituitary suppression and embryological outcomes in donor IVF cycles. PPOS is a clinically safe and effective alternative to traditional antagonist regimens.

Keywords: progestin-primed stimulation; GnRH antagonist; LH suppression; IVF; blastocyst

MÜLLERIAN ANOMALIES: CURRENT PRACTICE AND GENETIC LANDSCAPE

ALLA VASH MARGITA, MD, FACOG, Ass. Prof.

Division of Pediatric and Adolescent Gynecology, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale New Haven Hospital, New Haven, Connecticut, USA

ABSTRACT

Müllerian anomalies (MAs) affect approximately 5.5% of women of reproductive age and up to 24.5% of women with a history of infertility and miscarriage. These congenital anomalies are characterized by incomplete or aberrant development of the female reproductive tract, including the uterus, cervix, and upper vagina. Clinical phenotypes range from mild variations, such as an arcuate uterus, to uterine duplication and, in extreme cases, complete absence of the uterus and upper vagina.

Diagnostic delay and misdiagnosis are typical and may lead to poor clinical outcomes, long-term complications (eg, endometriosis), and impaired patient satisfaction. It is imperative to increase awareness and the ability to suspect and diagnose MAs among primary care providers and general obstetrician-gynecologists. Concomitant anomalies are frequent and range from renal anomalies to skeletal, cardiac, and auditory disorders.

Clinical management may vary from supportive care (eg, arcuate uterus) to complex long-term care requiring advanced surgical procedures, such as vaginoplasty or uterine transplantation (for Mayer-Rokitansky-Küster-Hauser syndrome or Müllerian aplasia). Optimal care for patients with MAs is best provided at centers of excellence with providers experienced in managing complex reproductive conditions. The psychological impact of MAs may be profound, depending on the specific anomaly, and require specialized support from skilled mental health professionals.

Research on the etiology of MAs is ongoing. Both genetic and environmental causes have been implicated. With advances in in vitro fertilization, surrogacy, and uterine transplantation, women with MAs may achieve biological motherhood. This underscores the importance of continued research into the genetic and hereditary patterns of MAs so that patients may be informed about the potential risk of transmitting a Müllerian anomaly to their female offspring.

Keywords: müllerian anomalies; reproductive tract malformations; Mayer-Rokitansky-Küster-Hauser syndrome; infertility; uterine transplantation

HORMONAL TREATMENT IN CATAMENIAL EPILEPSY: A CASE REPORT

TATIA VASHAKMADZE, MD, Resident;¹ **MARINA KVELIDZE**, MD, Resident;
GIORGI TSKRIALASHVILI, MD, Reproductologist²

¹ Anima Clinic, Tbilisi, Georgia

² Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Catamenial epilepsy refers to seizure exacerbation during specific phases of the menstrual cycle, most commonly the perimenstrual period. It remains underdiagnosed, **despite affecting** up to 60% of women with epilepsy. Hormonal therapy may offer significant benefit in such cases, especially when conventional antiepileptic drugs fail to provide **complete** seizure control.

Objective: To describe a case of catamenial epilepsy in a young woman with well-controlled focal epilepsy, presenting with seizure recurrence exclusively during menstruation, and to evaluate the effect of cyclic progesterone therapy.

Materials and Methods: A 24-year-old **woman**, diagnosed with epilepsy and treated with levetiracetam (500 mg/day), reported recurrent seizures over the past 2-3 years, occurring solely during menstruation. Each cycle was marked by a single generalized tonic-clonic seizure during the 4-day menstrual phase, while **she remained seizure-free during other phases**. Diagnostic evaluations confirmed focal epilepsy. The patient was started on oral dydrogesterone (Duphaston) 10 mg twice daily from day 15 to day 26 of the menstrual cycle (12 days/month).

Results: Following the introduction of cyclic progesterone therapy, the patient reported **complete** seizure control **from** the second treatment cycle, with no further seizures during menstruation. She remained seizure-free on continued combined antiepileptic and hormonal therapy.

Conclusions: This case highlights the **importance** of identifying catamenial patterns in women with epilepsy. Hormonal therapy using cyclic progesterone proved to be a successful and well-tolerated adjunctive treatment. Early recognition and individualized management may significantly improve the quality of life **of women** affected by catamenial epilepsy.

Keywords: catamenial epilepsy; progesterone therapy; levetiracetam; menstrual seizures; hormonal treatment

BACTERIAL BIOFILMS IN CHRONIC INFLAMMATION: A HIDDEN FACTOR IN REPRODUCTIVE FAILURE AND THE EXPANDING ROLE OF ENZYME, HORMONAL, AND MICROBIOME-BASED THERAPIES

LILIT MISAKYAN, MD

Center of Medical Genetics and Primary Health Care, Yerevan, Armenia

ABSTRACT

Background: As both a clinician and a biochemist, I have witnessed how many patients labeled with “unexplained infertility” are silently affected by chronic inflammation driven by persistent bacterial biofilms. These matrix-embedded microbial communities resist antibiotics, evade immune surveillance, and trigger low-grade inflammatory responses that are often overlooked during standard gynecological evaluations.

Over the years, I have managed challenging cases involving recurrent implantation failure, endometrial hostility, and pelvic adhesions, only to discover that biofilms were the missing factor. Beyond driving inflammation, biofilms also modulate hormone metabolism. Bacterial β -glucuronidase, produced within biofilms, can deconjugate estrogen metabolites in the gut and endometrium, leading to reactivation of estrogens, hyperestrogenism, and dysregulation of hormonal balance.

In addition, many of these patients presented with coagulopathies, ranging from prothrombotic states to subtle clotting irregularities, which further impair endometrial receptivity and placental development. I will present real cases where enzyme therapy (including rectal and vaginal administration of streptokinase, streptodornase, and longidase) was successfully applied to dissolve biofilms, reduce inflammation-induced coagulation disorders, and restore balanced endometrial perfusion.

A detailed case will be discussed in which full-cycle therapy, combining enzymatic treatment, anti-inflammatory agents, targeted probiotics, and PRP therapy, led step by step to biofilm clearance, hormonal balance, improved coagulation, and ultimately reproductive recovery.

The critical role of probiotics will also be emphasized. Optimal timing, strain selection (e.g., *Lactobacillus crispatus*, *L. acidophilus*, *Bifidobacterium*), and post-biofilm combination strategies will be addressed. These microbes are vital for re-establishing mucosal immunity and preventing recurrence.

This presentation provides an integrative framework uniting biofilm biology, hormonal metabolism, coagulopathy management, microbiome restoration, and PRP-based regeneration

– supported by clinical cases, ultrasound imaging, and biochemical monitoring. My goal is to empower clinicians to look beyond surface pathology and consider the biochemical and microbial architecture of the reproductive system, thereby expanding therapeutic options for complex infertility.

Keywords: bacterial biofilms; chronic inflammation; infertility; reproductive failure; hormonal metabolism; coagulopathy; enzyme therapy; microbiome; probiotics; PRP therapy

PCOS PHENOTYPES: A NEW LENS ON AN OLD SYNDROME

LALI PKHALADZE, MD;^{1,2} VITTORIO UNFER, MD^{2,3}

¹ Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

² The Experts Group on Inositol in Basic and Clinical Research, and on PCOS (EGOI-PCOS), Rome, Italy

³ AGUNCO Obstetrics & Gynecology Centre; UniCamillus-Saint Camillus International University of Health Sciences, Rome, Italy

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting 6%-18% of women worldwide, with diverse hormonal, metabolic, and reproductive implications. Since its initial description by Stein and Leventhal in 1935, the etiopathogenesis and diagnostic approach of PCOS have remained subjects of ongoing debate.

Objective: To evaluate evolving perspectives on PCOS classification and introduce mechanism-driven models that may improve individualized management.

Materials and Methods: The internationally endorsed Rotterdam criteria, updated in 2023, define PCOS by the presence of at least two of the following: ovulatory dysfunction (OD), clinical or biochemical hyperandrogenism (HA), and polycystic ovarian morphology (PCOM) or elevated anti-Müllerian hormone (AMH). This framework yields four phenotypes: A (OD+HA+PCOM), B (OD+HA), C (HA+PCOM), and D (OD+PCOM). Recent genome-wide association studies (GWAS) have identified distinct reproductive and metabolic PCOS subtypes with specific genetic architectures, highlighting the biological heterogeneity of the syndrome and the limitations of symptom-based classifications.

Results: The Georgian PCOS classification, developed by the Zhordania Institute of Human Reproduction, provides a pathogenetic framework distinguishing three main clinical forms: classical-genetically determined, hypothalamic, and ovarian-adrenal, and emphasizes individualized therapeutic approaches. Emerging evidence also underscores the central role of insulin resistance (IR) in driving hyperandrogenism and ovarian dysfunction in PCOS. In response, the Experts Group on Inositol in Basic and Clinical Research, and on PCOS (EGOI-PCOS) has proposed a mechanism-based classification:

- Endocrine Metabolic Syndrome (EMS) type 1: HA, IR, PCOM, and menstrual irregularities (resembles phenotype A).

- EMS type 2: HA, IR, PCOM, but without menstrual disturbances (resembles phenotype C).
- EMS type 3: Same features as type 1, but without PCOM (resembles phenotype B).
- Multi-Follicular Ovarian Disorder (MFOD): PCOM and menstrual dysfunction without HA or IR (resembles phenotype D).

All EMS phenotypes may present clinical signs of hyperandrogenism (acne, alopecia, hypertrichosis) and increased metabolic risks (diabetes, hypertension, infertility), while normoandrogenic MFOD lacks typical metabolic changes and is primarily associated with impaired ovarian physiology.

Conclusion: The EGOI-PCOS classification, by integrating endocrine, metabolic, and morphological parameters, represents a paradigm shift toward personalized, mechanism-driven diagnosis and management of PCOS.

Keywords: polycystic ovary syndrome (PCOS); PCOS phenotypes; endocrine-metabolic syndrome (EMS); hyperandrogenism; insulin resistance; EGOI-PCOS classification

ADIPOSE TISSUE AND REPRODUCTIVE HEALTH: MECHANISTIC INSIGHTS AND CLINICAL IMPLICATIONS IN OVERWEIGHT AND OBESE PATIENTS

NUNU RAZMADZE, *Resident*

*Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology,
Tbilisi, Georgia*

ABSTRACT

Background: “Weight loss” is among the most frequently recommended medical interventions and is known to exert a profound impact on reproductive health. A significant number of patients diagnosed with infertility conceive solely through weight reduction, underscoring the importance of understanding how adipose tissue influences reproductive function. This highlights the critical need to investigate the mechanistic pathways through which adiposity affects the reproductive systems of both females and males.

Objective: To comprehensively review the literature – from core medical textbooks to recent peer-reviewed articles – to synthesize current knowledge on the endocrine, paracrine, and inflammatory properties of adipose tissue.

Materials and Methods: This review is based on a thorough literature search, utilizing sources such as PubMed, Elsevier, and UpToDate. Emphasis is placed on integrating both foundational physiological concepts and current findings regarding the molecular and systemic effects of adipose tissue on reproductive health.

Results: While anovulation remains the most frequently recognized mechanism linking obesity to female infertility, it is not the only one. A substantial number of overweight or obese women maintain regular ovulatory cycles yet still experience infertility. In such cases, chronic low-grade inflammation, mediated by adipocyte-derived cytokines, appears to compromise reproductive tract function. Additionally, psychological factors, including body image dissatisfaction, may contribute to sexual dysfunction and decreased fertility.

Although the majority of existing literature focuses on female reproductive health, male fertility is also highly susceptible to the effects of excess adiposity. Given the shared dependence of both sexes on the hypothalamic-pituitary-gonadal (HPG) axis, obesity-induced hormonal imbalance, impaired spermatogenesis, and erectile dysfunction, often intertwined with psychological distress, represent significant barriers to male reproductive success.

Conclusion: A comprehensive understanding of the reproductive consequences of overweight and obesity is essential, not only for treating patients with infertility or hormonal imbalance but also for effective preventive education. As obesity continues to rise globally, it is imperative for healthcare providers to fulfill their role as health advocates by promoting awareness and prevention of weight-related reproductive dysfunction across the population.

Keywords: obesity; reproductive health; anovulation; sexual dysfunction; adipose tissue

MODERN APPROACHES TO THE TREATMENT OF UNEXPLAINED INFERTILITY: INDIVIDUALIZED PROTOCOLS, NOVEL MARKERS, AND BIOTECHNOLOGIES

SAMIRA TAGHIYEVA, PhD

Oksigen Clinic, Baku, Azerbaijan

ABSTRACT

Background: Unexplained infertility (UI) is a diagnostic category in which no apparent cause of reproductive dysfunction is identified despite thorough evaluation. UI accounts for approximately 10-30% of all infertility cases. Contemporary reproductive medicine emphasizes personalized treatment strategies, advanced diagnostics, and molecular-level interventions.

Individualized Treatment Protocols

Pharmacogenetics: Genetic polymorphisms (e.g., FSH receptor mutations) influence ovarian response to stimulation and allow for precise dosage adjustments and medication selection. **Personalized Ovarian Stimulation:** Protocol choice (antagonist, long, or mild stimulation) is tailored based on AMH levels, antral follicle count (AFC), and patient history. Mild stimulation protocols reduce the risk of ovarian hyperstimulation syndrome (OHSS) while preserving outcomes.

Biomarkers and Expanded Diagnostics

Endometrial Biomarkers: The Endometrial Receptivity Array (ERA test) evaluates the timing of the implantation window, guiding optimal embryo transfer. **Immunological Factors:** Evaluation of natural killer (NK) cell activity, cytokine levels (e.g., IL-6, TNF- α), and HLA compatibility may reveal subtle immune dysfunctions. Immunomodulators can be applied in cases of immune imbalance. **Proteomics and Metabolomics:** Analysis of follicular fluid and endometrial secretions helps identify hidden dysfunctions that impact oocyte quality or embryo implantation potential.

Emerging Technologies and Therapies

Genetic and Molecular Tools: PGT-A (preimplantation genetic testing for aneuploidy) and non-invasive PGT-A (niPGT-A) allow for genetic screening of embryos without biopsy. **Microbiome Studies:** Alterations in the vaginal or endometrial microbiome may impair implantation; mod-

ulation with probiotics or antibiotics is under study. Novel Therapies: Platelet-rich plasma (PRP) therapy – intrauterine PRP infusion stimulates endometrial growth and regeneration. Endometrial scratch – mechanical stimulation may promote receptivity (evidence remains inconclusive). Antioxidant therapy (coenzyme Q10, vitamin D, melatonin) is used as supportive treatment in selected cases.

Materials and Methods: We analyzed treatment outcomes of 47 patients with unexplained infertility (UI) who were followed at Oksigen Clinic (Baku, Azerbaijan) between 2018 and 2024.

All patients underwent:

- Comprehensive hormonal and ultrasound evaluation
- Reproductive microbiome assessment (RT-PCR, NGS)
- Endometrial immune profiling (analysis of NK cell activity and cytokine levels)
- ERA testing (Endometrial Receptivity Array) in 29 patients
- Individualized ovarian stimulation protocols
- Adjunctive therapies including PRP, antioxidant therapy, probiotics

Results:

- Immune dysregulation (elevated NK cell activity and cytokine imbalance) was detected in 28 patients (60%).
- Vaginal and/or endometrial microbiota alterations were diagnosed in 14 patients (30%), including reduced *Lactobacillus* spp. and overgrowth of conditionally pathogenic flora.
- ERA testing was performed in 21 women (45%), with a displaced implantation window identified in 15 cases (71%).

After personalized correction (immunotherapy, PRP, probiotics, optimized embryo transfer timing):

- Clinical pregnancy was achieved in 33 of 47 patients (70.2%).
- 18 of 21 patients conceived following endometrial receptivity correction.
- 13 patients conceived after two or more failed IVF attempts in other clinics.

Conclusions: Unexplained infertility requires a multidisciplinary and individualized approach. Advances in molecular diagnostics, immunological assessment, and microbiome research have created new opportunities for targeted treatment. Transitioning from empirical therapies to evidence-based, precision medicine has demonstrated promising improvements in clinical outcomes for patients with unexplained infertility.

Keywords: unexplained infertility; personalized protocols; endometrial receptivity; immunological factors; reproductive microbiome; PRP therapy; precision medicine

UNVEILING THE ROLE OF BACTERIOPHAGES IN GYNECOLOGY: A SYSTEMATIC REVIEW AND CASE-BASED ANALYSIS

NATA NAKAIDZE, MD;^{1,2} IRMA TEDORADZE, MD;² DEA NIZHARADZE, MD²

¹ Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

² Eliava Phage Therapy Center, Tbilisi, Georgia

ABSTRACT

Background: The female reproductive tract (FRT) harbors a complex ecosystem of commensal microorganisms, including bacteria, viruses, archaea, and fungi. While the bacterial component of the FRT has been well studied, the viral component – particularly bacteriophages – remains underexplored. The risk of bacterial vaginosis (BV) increases with disruption of the vaginal microbiome and the loss of protective *Lactobacillus* species. BV is a complex clinical challenge with high recurrence rates and is associated with increased susceptibility to gynecological and obstetric complications.

Objective: To elucidate the role of bacteriophages in regulating bacterial communities and maintaining microbial homeostasis within the FRT, with particular focus on BV pathogenesis. We also aimed to explore the therapeutic potential of bacteriophages against urogenital infections, drawing on clinical cases from the Eliava Phage Therapy Center.

Materials and Methods: A systematic descriptive review was performed, encompassing peer-reviewed publications, including research articles and review papers. In addition, clinical case reports were analyzed, with direct patient management involvement.

Results: Emerging evidence suggests that bacteriophages influence the stability and composition of the vaginal microbiome, contributing to both the development and resolution of BV. Moreover, phages can be utilized therapeutically: when pathogenic bacteria are identified, specific bacteriophages can be selected based on in vitro sensitivity to effectively target and eliminate these strains. Therapeutic approaches include both mono-phage preparations and phage cocktails designed to optimize efficacy against diverse or resistant bacterial profiles.

Conclusions: Temperate bacteriophages play a key role in microbiome networks by directly influencing *Lactobacillus* populations through prophage formation. The antibacterial activity of lytic bacteriophages can also be harnessed to selectively target pathogenic bacteria, offering promising approaches to urogenital tract infections. The role of bacteriophages in gynecology is significant, and current research indicates we are on the cusp of critical discoveries in this field.

Keywords: FRT virobiome; commensal viruses; bacterial vaginosis; bacteriophage therapy; transkingdom interactions

PREGNANCY FOLLOWING CRANIOPHARYNGIOMA RESECTION AND PITUITARY ATROPHY: A RARE MEDICAL CASE

NUTSA CHIGLADZE, Resident
Gagua Clinic, Tbilisi, Georgia

ABSTRACT

Craniopharyngiomas are rare, benign intracranial tumors that can lead to significant endocrine dysfunction due to damage to the hypothalamic-pituitary axis. Successful pregnancy in women with long-standing panhypopituitarism and pituitary atrophy is highly uncommon and requires complex, multidisciplinary management.

Objective: To present a rare case of successful pregnancy in a patient with panhypopituitarism and an empty sella turcica following childhood craniopharyngioma resection.

Materials and Methods: We report a 43-year-old woman with a history of craniopharyngioma diagnosed at age 13, followed by surgical resection at age 14, resulting in pituitary atrophy and empty sella syndrome. She developed panhypopituitarism, including secondary hypothyroidism, adrenal insufficiency, hypogonadism, growth hormone deficiency, and transient diabetes insipidus. Long-term hormone replacement therapy included levothyroxine, corticosteroids, and sequential estrogen-progestin therapy. IVF with donor oocytes and partner sperm was planned after hysteroscopic correction of an incomplete uterine septum. Hormonal support during implantation and pregnancy was provided with estradiol, dydrogesterone, and multiple forms of progesterone. Corticosteroid and thyroid hormone doses were adjusted during gestation.

Results: After the second embryo transfer, pregnancy was confirmed. Management was complicated by recurrent vaginal bleeding requiring prolonged progesterone support, polyuria (without confirmed diabetes insipidus), and gestational hypertension treated with methyldopa. At 37+3 weeks, due to uncontrolled hypertension and breech presentation, an emergency cesarean section was performed, delivering a live female infant weighing 2600 g, Apgar score 8/8. Postpartum recovery was uneventful.

Conclusion: This case illustrates that, despite severe pituitary dysfunction and uterine hypoplasia, a successful pregnancy is achievable through optimized hormone replacement, surgical correction of uterine anomalies, and IVF with donor gametes. Early initiation of combined gonadotropin and growth hormone therapy in adolescence could have improved ovarian development and fertility potential.

Keywords: craniopharyngioma; empty sella syndrome; panhypopituitarism; hormone replacement therapy; IVF pregnancy

ANTICOAGULANTS IN RECURRENT PREGNANCY LOSS

HOWARD CARP, J. A. MB., BS. MRCOG

*Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer;
and Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

Background: Anticoagulants, including Aspirin and Low molecular weight heparins (LMWH), are often used as a preventive treatment for women with recurrent pregnancy loss, particularly in cases where thrombophilia is suspected or confirmed. The rationale is that thrombosis in decidual vessels can restrict the blood flow to the placenta, leading to pregnancy loss. Several studies suggest that LMWH, possibly in combination with aspirin, may improve pregnancy outcomes, particularly when antiphospholipid syndrome (APS) or other clotting disorders are involved. However, the use of LMWH for miscarriage prevention is dubious in unexplained pregnancy loss.

Material and Methods: Medline, Embase, and Ovid Medline were searched for original reports with the product names 'Aspirin', LMWH, Heparin, Enoxaparin, and Fragmin, and limited to clinical human data.

Results: Previous meta-analyses have shown anticoagulants to be effective in antiphospholipid syndrome (5 Trials). However, the literature has been disputed. Aspirin was not found to confer any additional beneficial effect. However, aspirin may confer additional benefit for the late complications of APS seen in pregnancy.

In hereditary thrombophilias, there was a greater prevalence of miscarriage and later obstetric complications. Obstetric complications were mainly found with Factor V Leiden and the prothrombin gene mutation (G20201A). Overall, meta-analysis has shown an improvement in the live birth rate when using LMWH. (OR 2.19 CI 1.56-3.04).

Aspirin was not found to have a beneficial effect in hereditary thrombophilia. (OR= 1.25, CI 0.86-1.82). However, there was a far greater incidence of bleeding episodes associated with aspirin use.

Likewise, in unexplained recurrent pregnancy loss, Aspirin does not affect the live birth rate in 6 studies and was only reported to be effective in one registry. Anticoagulants have been reported to raise the live birth rate in women with unexplained RPL. However, many of the

positive trials have been retracted or had expressions of concern about the methodology. The author has found seven high-quality studies assessing anticoagulants in unexplained RPL. Only one study showed a significant benefit.

Conclusions: Aspirin has not been shown to reduce first-trimester miscarriage rates in APS, hereditary thrombophilias, or unexplained pregnancy losses. Its use remains limited to the prevention of preeclampsia. In APS and hereditary thrombophilias, anticoagulants raise the live birth rate. Newer forms of treatment, such as Hydroxychloroquine, Tacrolimus, and statins, need further trials to assess efficacy.

Keywords: anticoagulants; recurrent pregnancy loss; aspirin; low molecular weight heparin (LMWH); antiphospholipid syndrome; hereditary thrombophilia

HCG: THE FORGOTTEN HORMONE IN RECURRENT PREGNANCY LOSS

HOWARD CARP, J. A. MB., BS. MRCOG

*Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer;
and Tel Aviv University, Tel Aviv, Israel*

ABSTRACT

Human chorionic gonadotrophin (hCG) is an essential hormone in the regulation of human pregnancy. hCG acts by endocrine, paracrine, and autocrine mechanisms that activate multiple cellular signaling pathways in gestational and non-gestational tissues. hCG has luteotrophic and uterine effects, including:- differentiation of endometrial stroma to decidua, regulation of myometrial gap junctions, prevention of T-cell activation at the materno-fetal interface, and modulation of cytokine expression. Our purpose was to assess whether hCG increases the live birth rate in women with Recurrent Pregnancy Loss.

A Cochrane systematic review of four trials showed that hCG was effective (OR for miscarriage = 0.51, 95% CI 0.32-0.81). Two additional trials were identified, including the author's trial. Our experience indicates a 28% benefit in women with ≥ 3 miscarriages, and a statistically significant 37% benefit in women with ≥ 5 miscarriages (OR = 3.44 (95% CI 1.3-9.0). The overall OR for a live birth from all of the studies was 2.65 (CI 1.60-4.44).

Only the author's trial was matched for prognostic factors such as the number of miscarriages, 1^o, 2^o, or 3^o aborter status, maternal age, etc. However, no correction was made for chromosomally abnormal pregnancies, which confound the results.

The results of this systematic review show a significant 2.25 increase in odds for a live birth. As previous trials used urinary hCG, the effect on pregnancy outcome may be attributable to hCG itself or urinary proteins such as leukemia inhibitory factors (LIF) and epidermal growth factor (EGF), etc., present in urinary preparations. Hence, a new trial is indicated in order to test hCG on a larger number of women with recurrent miscarriage. Treatment and placebo arms must be stratified for prognostic factors, and the results corrected for fetal chromosomal aberrations. Until such a trial is mounted, the use of hCG supplements is empirical.

Keywords: human chorionic gonadotrophin (hCG); recurrent pregnancy loss; live birth rate; systematic review; urinary hCG therapy; chromosomal aberrations

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GENETIC/FAMILIAL HIGH-RISK ASSESSMENT: BREAST & OVARIAN CANCER

TEVFIK YOLDEMIR, MD, MA, PhD, Prof.

Obstetrics and Gynecology, Marmara University, School of Medicine, Turkey

ABSTRACT

The identification of pathogenic and likely pathogenic variants (P/LPV) in high- and moderate-penetrance genes can impact treatment strategies, surveillance, and preventative surgeries. High-penetrance gene P/LPVs, however, often lead to significant changes in the functions of the associated protein products and are associated with higher risks for cancer development than in the general population. Testing high-penetrance genes in selected individuals has clinical utility, such as informing medical decision-making and helping to prevent or decrease adverse health outcomes.

An estimated 10% of breast cancer occurs in the setting of hereditary, single-gene P/LPVs such as those within *BRCA1* and *BRCA2*. About 18% of all ovarian cancers have been associated with *BRCA1* or *BRCA2* P/LPVs, while another 6% have been attributed to variants in other genes. In the general population, approximately 12% of women will develop breast cancer at some point in their lives, while approximately 1.3% will develop ovarian cancer. Identifying those who do carry P/LPVs is critical for patients and their potentially at-risk family members.

The prevalence of *BRCA* P/LPVs have shown: 0.2 to 0.3% of the general population carry P/LP variations in these genes, including 3% of women with breast cancer, 6% of women with breast cancer onset prior to 40 years of age, 10% of women with ovarian cancer at any age, and 20% of high-risk families. Women with germline *BRCA1* P/LPVs are estimated to generally thought to face a 60%-72% risk of breast cancer to age 70, while those with *BRCA2* P/LP are estimated to have a 55%-88% risk. The ovarian cancer incidence by age 70 is 44%-59% in *BRCA1* P/LPV carriers and 17%-35% in *BRCA2* carriers. The 10-year risk for contralateral breast cancer is 17%-34% in women with *BRCA1* P/LPVs, and 7%-30% in those with *BRCA2* P/LPVs.

Breast cancers can also be associated with P/LPVs in some moderate- and low-risk genes such as *PALB2*, *CHEK2*, and *ATM*. An estimated relative risk of breast cancer of 2.8 for *ATM* P/LPVs and 3.0 for *CHEK2* P/LPVs, including lower-risk missense variants, was reported. Ovarian cancer can be associated with variants in other 'breast cancer genes' such as *BARD1*, *BRIP1*, *CHEK2*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53*.

There are several clinical clues to look for when considering the presence of a hereditary susceptibility to cancer. These include, but are not limited to: a. cancer occurring at an earlier than average age (e.g., premenopausal breast cancer), b. multicentric development of cancer in the same organ and/or bilateral development of cancer in paired organs, c. development of more than one primary cancer, associated with cancer predisposition genes, in a single individual; important exceptions should be noted for common cancers with clear non-inherited etiologies, such as non-melanoma skin cancers, lung cancer, and cervical cancer, d. clustering of cancers consistent with a specific syndrome (e.g., breast and ovarian), e. cancer of the same type in two or more relatives (on the same side of the family), f. excess number of cancers in the family, g. particular ethnic groups known to be at higher risk of hereditary cancer (e.g., *BRCA1/2* P/LPVs in Ashkenazi Jewish populations), h. familial cancer diagnoses suggestive of an autosomal dominant pattern, i. rare tumors with a strong association with specific cancer syndromes or a significant heritable component, such as male breast cancer, adrenocortical carcinoma, etc.

P/LPVs in high- and moderate-risk breast cancer genes account for a portion of breast cancer risk; however, other factors can increase a woman's risk. These other factors include family history, reproductive history, lifestyle factors, and previous exposure to thoracic radiation. While having had previous breast biopsies is a marker for increased cancer risk, it is not, itself, a risk factor.

Management of patients at increased risk for breast and ovarian cancer remains a challenge for healthcare professionals. Various guidelines and recommendations have been published regarding the management of patients considered to be at significantly increased risk for breast and ovarian cancer. For appropriate patients, recommendations include surveillance as well as consideration of chemoprevention and risk-reducing surgeries.

Keywords: hereditary breast and ovarian cancer; pathogenic/likely pathogenic variants (P/LPVs); *BRCA1*; *BRCA2*; genetic testing; cancer risk management

Reference

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EFFECTIVENESS OF COMBINED SURGICAL AND HORMONAL THERAPY IN TREATMENT OF ENDOMETRIOMAS

EKATERINE CHIKHASHVILI, MD, PhD Student;¹ **JENARO KRISTESASHVILI**, MD, PhD, Prof.;² **MAIA URJUMELASHVILI**, MD, PhD, Ass. Prof.³

¹ Department of Clinical and Research Skills, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

² Department of Obstetrics, Gynecology and Reproductology, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

³ Faculty of Medicine, University Geomedi, Tbilisi, Georgia

ABSTRACT

Background: The high recurrence rate of endometriomas after surgery presents a significant challenge in their management.

Objective: To evaluate the effectiveness of combined surgical and hormonal therapy of endometriomas in terms of recurrence, pregnancy rate, and changes in pain intensity.

Materials and Methods: A total of 264 patients with endometriomas who underwent laparoscopic enucleation of endometrial cysts were observed for 5 years post-surgery. Patients were divided into four groups: Group I – dienogest for 6 months continuously (n = 58); Group II – combined oral contraceptives (COCs) for 6 months cyclically (n = 62); Group III – dydrogesterone for 6 months cyclically (n = 45); Group IV – control group, no postoperative hormonal treatment (n = 99).

Results: Pregnancy rate was significantly higher in Group I (72.4%, $P < 0.01$) compared to controls (34.8%) and Group III (47.2%, $P < 0.05$). No significant difference was found between Group III and controls ($P > 0.05$). Pregnancy rate could not be assessed in Group II since no patients desired pregnancy. Endometrioma recurrence was absent in Groups I and II, 1.6% in Group III, and significantly higher in controls (18.2%, $P < 0.01$). Severe pain was reduced to moderate in 59.4% of Group I, 44.5% of Group II, 76.2% of Group III, and 93.7% of controls; complete pain resolution was observed in 40.6%, 55.5%, 23.8%, and 6.3%, respectively. Dienogest and COCs were significantly more effective than dydrogesterone ($P < 0.05$) or surgery alone ($P < 0.05$). In patients with moderate pain, persistence was observed in 0% (Group I), 3.8% (Group II), 16% (Group III), and 46.9% of controls. All hormonal therapies were more effective than surgery alone ($P < 0.05$). No significant differences were observed between hormonal regimens ($P > 0.05$).

Conclusions: Combined therapy (surgery followed by hormonal treatment) for endometriomas is significantly more effective than surgery alone in reducing recurrence and pain intensity and in improving pregnancy outcomes.

Keywords: endometrioma; recurrence; dienogest; hormonal therapy; fertility

IVF AND BREAST CANCER: MYTHS AND REALITY

NINO CHIKOBAVA, MD, PhD, Prof.

*General Surgeon; Surgical Oncologist; Mammologist; Assistant Professor,
Georgian-German Reproduction Centre, Tbilisi, Georgia*

ABSTRACT

Background: The use of assisted reproductive technologies (ART), particularly in vitro fertilization (IVF), has increased significantly in recent decades. Alongside its growth, concerns have emerged regarding the potential long-term health risks associated with hormonal stimulation, especially the risk of hormone-sensitive malignancies such as breast cancer.

Objectives: To critically evaluate the current evidence regarding a potential association between IVF and breast cancer risk, to dispel common misconceptions, and to support evidence-based decision-making in clinical practice.

Methods: A comprehensive review of the literature was conducted, including recent meta-analyses, cohort studies, and population-based data. We examined studies with varied IVF protocols, durations of follow-up, and patient subgroups, including women with genetic predisposition (e.g., BRCA mutations) and those undergoing repeated cycles.

Results: The majority of large-scale studies do not show a statistically significant increase in breast cancer risk following IVF, particularly in women without predisposing genetic factors. Some studies suggest a transient or weakly elevated risk in specific subgroups, but these findings often lack consistent replication and may be influenced by confounding variables such as age, parity, and indication for infertility treatment.

Conclusion: Current evidence does not support a definitive causal relationship between IVF and breast cancer. Nevertheless, ongoing surveillance and individualized risk assessment remain essential, particularly for high-risk patients. Addressing misinformation and fear-based narratives is crucial for guiding patients through informed reproductive decisions grounded in science rather than speculation.

Keywords: in vitro fertilization; assisted reproductive technology; breast cancer; BRCA mutations; infertility treatment

FERTILITY AFTER UNILATERAL OOPHORECTOMY

STELA DZOTSENIDZE, MD, PhD Student
Silk Medical Clinic, Tbilisi, Georgia

ABSTRACT

Background: Unilateral oophorectomy (UO), commonly performed for benign ovarian cysts, torsion, or ovarian endometriosis, raises concerns about its long-term impact on ovarian reserve and fertility – especially in young patients. The compensatory ability of the remaining ovary is not well established across age groups.

Objective: To assess ovarian function and fertility outcomes following UO across different age groups.

Materials and Methods: A retrospective-prospective study was conducted on 43 females (ages 7-38) who underwent UO. Patients were grouped by age at surgery: Group I (7-15 y), Group II (16-30 y), Group III (30-38 y). Menstrual patterns and serum hormone levels (AMH, FSH, LH, TSH, PRL) were evaluated at three time points: immediately after surgery, three months, and one year postoperatively.

Results: The mean participant age was 26.74 y; the mean age at surgery was 21.58 y. Right-sided UO was more common (65.1%). Indications included follicular cysts in 52%. Menstrual irregularities were more frequent in Groups I and III after surgery. AMH levels dropped postoperatively but recovered within a year in Groups I and II, indicating age-dependent ovarian compensation. Group III showed persistent AMH suppression.

Conclusions: UO does not significantly impair fertility potential, particularly in younger patients. Despite transient hormonal fluctuations, the contralateral ovary generally maintains functional competence to support reproductive health. Fertility counseling is recommended post-surgery.

Keywords: Unilateral oophorectomy, ovarian reserve, AMH, fertility preservation, reproductive outcomes, ovarian function

CURRENT STATE OF IVF IN GEORGIA: TRENDS AND CHALLENGES

NATALIA KHONELIDZE, PhD, Prof.; ¹ **GIA TSAGAREISHVILI**, PhD, Prof.; ¹ **MAIA KOIAVA**²

¹ Tbilisi State Medical University (TSMU), Tbilisi, Georgia

² Senior Embryologist

ABSTRACT

In vitro fertilization (IVF) and third-party reproduction have undergone a remarkable global transformation over the past two decades, driven by cutting-edge technologies and evolving ethical frameworks. It has been 25 years since the birth of the first IVF baby in the South Caucasus, specifically in Georgia. Georgia, a small nation in the South Caucasus, has emerged as a regional leader in assisted reproductive technologies (ART), offering modern clinical capabilities, legal openness, and cost-effective services.

The aim of this review is to present and describe current demographic trends in Georgia and to provide a technological overview of in vitro fertilization methods. Such analysis will help implement innovative laboratory technologies and prepare for emerging global challenges in reproductive medicine.

IVF technology in Georgia is developed to the same high standards as in the world's leading clinics. This review examines the current state of IVF in Georgia, focusing on the adoption of advanced laboratory technologies – including embryo vitrification, intracytoplasmic sperm injection (ICSI), embryo biopsy, preimplantation genetic testing (PGT), and related genetic testing. Leading clinics in Georgia operate with equipment and protocols aligned with European standards, although regional disparities and a lack of regulation persist.

The growing demand for assisted reproductive technologies is driven not only by socio-demographic trends but also by the relatively flexible legal framework surrounding IVF in Georgia. There are around 200,000 infertile couples of reproductive age in Georgia, 10% of whom require IVF treatment. Legislative flexibility has played a key role in promoting medical tourism, particularly in egg donation and surrogacy. Georgia has become a growing hub for medical tourism in the Caucasus region and beyond. Over the last 5 years, the number of international patients seeking IVF and surrogacy services in Georgia has increased significantly.

This topic highlights the intersection of technological progress, international demand, and policy gaps in Georgia's IVF ecosystem. It emphasizes the need to strengthen regulatory oversight, ensure ethical consistency, and support sustainable growth of ART services while balancing innovation with responsibility.

Keywords: IVF; ART; third-party reproduction; medical tourism

COMPLEX/COMBINED TREATMENT OF WOMEN WITH VAGINISMUS: EVIDENCE-BASED STUDY

ZURAB MARSHANIA, Prof.; ¹ **NINO NODIA**, PhD Candidate^{1,2}

¹ Professor Zurab Marshania Medical Sexology Office, LLC, Tbilisi, Georgia

² Doctor reproductologist, obstetrician, gynecologist

ABSTRACT

Background: Vaginismus is a female sexual dysfunction classified as a rare disorder, defined by recurrent or persistent involuntary spasm and contraction of the musculature of the outer third of the vagina during attempted vaginal penetration, associated with fear of sexual intercourse. Sometimes spasms and contractions of the pelvic, abdominal, and hip muscles also occur, together with pain that interferes with vaginal penetration and prevents complete penile entry into the vagina.

Objectives: The purpose of this study was to evaluate the success rate of complex/combined treatment of vaginismus among women, depending on disease severity and the psychological type of patients with vaginismus.

Methods: This prospective study included 246 Georgian women diagnosed with vaginismus, all treated by physician-sexologist Prof. Z. Marshania. The mean age of the patients was 27.2 years. A gynecologist consulted all patients. They completed scales assessing pain, cramps and spasms, and fear before and after treatment. In 32 women, psychodiagnostic examination was performed to determine the severity of anxiety disorder using Spielberger's test. Complex and combined treatment of vaginismus included:

1. Conservative therapy with selective serotonin reuptake inhibitors and local procedures (hot baths in the pelvic area and vaginal suppositories with hyaluronidase).
2. Psychotherapeutic intervention using the "Sensate Focus" method, modified by Prof. Z. Marshania.
3. Cognitive psychotherapeutic intervention aimed at facilitating successful first vaginal penetration.

Results: Treatment success was achieved in 91.5% (225) of patients, all of whom were able to begin regular vaginal sexual intercourse. In 21 women (8.5%), treatment was unsuccessful. Improvement in vaginismus symptoms – including spasm/contraction, fear, and pain – as well as a reduction in the severity of anxiety disorder, was statistically confirmed ($P < 0.001$) by paired-sample test (SPSS).

Conclusion: The high success rate achieved in this study indicates that the proposed method deserves attention as a potential "gold standard" in the treatment of patients with vaginismus.

Keywords: vaginismus; sexual dysfunction; cognitive psychotherapy; sensate focus; combined treatment

WEIGHT AS A MODULATOR OF HORMONAL AND METABOLIC PATTERNS IN CLASSIC PCOS ACROSS AGE GROUPS

**ELISABED PKHALADZE, MD;¹ LALI PKHALADZE, MD;² NINO DAVIDOVA, MD;²
NANI KVASHILAVA, MD;² ARCHIL KHOMASURIDZE, MD, PhD, Prof.²**

¹ David Tvildiani Medical University, Tbilisi, Georgia

² Prof. Zhordania and Prof. Khomasuridze Institute of Reproductology, Tbilisi, Georgia

ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common multifactorial endocrine disorder. Body weight significantly modulates the clinical and metabolic features of PCOS across the lifespan. A weight-sensitive approach to diagnosing and managing PCOS enables personalized care that addresses both metabolic and reproductive concerns.

Objective: To evaluate weight-associated hormonal and metabolic parameters in adolescents and adults with classic PCOS.

Methods: This cross-sectional observational study included 52 patients aged 12-35 years with classic PCOS, categorized into adolescents (Group A) and adults (Group B). Each group was further divided based on weight: lean adolescents (AI, n=13); lean adults (BI, n=15); overweight/obese adolescents (AII, n=12); overweight/obese adults (BII, n=12). Anthropometric, clinical, and hormonal parameters were evaluated. Descriptive statistical analyses were conducted (SPSS v26.0).

Results: Overweight/obese adolescents and adults demonstrated significantly higher insulin, glucose, and HOMA-IR levels compared with their lean counterparts. Hyperinsulinemia and insulin resistance were observed in 15% of lean adolescents and 40% of lean adults, compared with 92% of overweight/obese adolescents and 83% of overweight/obese adults. No significant differences in testosterone, free androgen index, LH/FSH ratio, or AMH levels were noted between lean and overweight/obese individuals within each age group. However, overweight/obese adults exhibited significantly elevated DHEA-S levels compared with lean adults, a pattern not observed in adolescent groups. AMH levels were higher in overweight/obese adolescents than in overweight/obese adults.

Conclusions: In patients with classic PCOS, weight is a key modulator of metabolic and hormonal patterns. Hyperinsulinemia and insulin resistance are strongly associated with excess weight across all age groups. Elevated DHEA-S levels in overweight/obese adults highlight age-specific patterns of androgen excess, whereas increased AMH levels in overweight/obese adolescents reflect more pronounced ovarian dysfunction.

Keywords: polycystic ovary syndrome (PCOS); obesity; insulin resistance; hyperinsulinemia; hyperandrogenemia; dehydroepiandrosterone sulfate (DHEA-S); anti-Müllerian hormone (AMH)

PREGNANCY RATE IN THE CASE OF MOSAIC EMBRYO TRANSFER

MARIAM SHERVASHIDZE, MD; THEA PATARAIA, MD; TAMAR BARBAKADZE, MD; TAMAR KBILASHVILI, MD; MARIAM GABADZE, MD; TEMIKO ZHORZHOLADZE, MD; NINO KUTCHUKHIDZE, MD;¹ LIA CHKONIA, MD
Georgian-American Center for Reproductive Medicine REPROART, Tbilisi, Georgia

ABSTRACT

Background: The identification of chromosomal mosaicism in preimplantation embryos via next-generation sequencing (NGS) during preimplantation genetic testing for aneuploidy (PGT-A) has introduced significant complexity into clinical decision-making in assisted reproductive technology (ART). Mosaic embryos, defined by the coexistence of two or more cell lines with distinct chromosomal constitutions, are typically identified through trophectoderm (TE) biopsy at the blastocyst stage. The clinical utility and safety of transferring such embryos remain under ongoing investigation.

Objective: To evaluate pregnancy outcomes following the transfer of embryos diagnosed as mosaic by PGT-A, and to assess the implications of mosaicism levels on implantation and pregnancy rates.

Materials and Methods: A retrospective analysis of 41 mosaic embryo transfer cases performed between 2023 and 2024 was conducted. Transfers were categorized based on the level of mosaicism, the number of embryos transferred, and whether mosaic embryos were transferred alone or alongside euploid or non-tested embryos.

Results: Of the 41 transfers, 23 involved only mosaic embryos (either single or double embryo transfers with low- or high-level mosaicism). Among these, 11 cases resulted in a positive β -hCG test, corresponding to a pregnancy rate of 47.8%.

Conclusion: Despite evidence suggesting reduced implantation potential and increased miscarriage risk compared to euploid embryo transfer, mosaic embryo transfer remains a clinically relevant option in the absence of euploid embryos. With appropriate patient counseling and informed consent, the transfer of mosaic embryos can be considered a viable strategy. Further large-scale studies are warranted to clarify the reproductive potential and clinical risks associated with mosaic embryo transfer.

Keywords: mosaic; PGT-A; pregnancy rate; embryo transfer; assisted reproductive technology

HORMONAL CORRECTION OF MENSTRUAL CYCLE DISORDERS (MCD): FOCUS ON SEX STEROIDS

GEORGE TEVDORASHVILI, MD, PhD;¹ MARIAMI ANDGULADZE, MD, PhD²

¹ Tbilisi State Medical University, First University Clinic, Tbilisi, Georgia

² Medicare Georgia, Tbilisi, Georgia

ABSTRACT

Background: Maintaining menstrual health plays a vital role in maintaining endocrine health function, reproductive and general health, and quality of life (QOL) in both adolescent girls and women of reproductive age.

Menstrual cycle disorders (MCDs), whose effects are not limited to women of reproductive age and lead to adverse health outcomes beyond reproductive age, significantly increases the burden of noncommunicable diseases for the general population worldwide.

Menstrual cycle disorders, their consequences, and the challenges of diagnosis, treatment, and future prospects vary across the reproductive stages of a woman's life, with differences in age, endocrine profile, demands, and risks.

Interventions: For the treatment of menstrual disorders, sex steroid hormonal medications are mainly used, both as monotherapy and in combination regimens.

Clinical challenges: The main challenges of the action of sex steroid drugs are the control of cycles and bleeding, the action on the central nervous system, and the control of urogenital and sexual changes. In some patients, the response to sex steroids is paradoxical.

It is important to carefully determine the selection of each of them, the choice of combined use, the route of administration, and the dosage regimen, as well as the duration of administration.

Future prospects: When making decisions regarding the choice of sex steroid hormones in the presence of menstrual cycle disorders (MCD), it is recommended to consider their impact on the overall quality of life, use an individualized approach for each patient, including the integration of pharmacogenetic characteristics, biomarkers, and artificial intelligence, and clearly define what, when, and how to use it to achieve the desired results – with minimized risks of side effects and complications.

Keywords: menstrual cycle disorders; sex steroids; hormonal therapy; reproductive health; quality of life; pharmacogenetics

მენსტრუალური ციკლის დარღვევების (MCD)

ჰორმონალური კორექცია:

ფოკუსირება სასქესო სტეროიდებზე

გიორგი თავდორაშვილი,¹ მარიამ ანდლულაძე²

¹ თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის პირველი საუნივერსიტეტო კლინიკა, თბილისი, საქართველო

² კლინიკა “მედიქა”, თბილისი, საქართველო

აბსტრაქტი

კონტექსტი: მენსტრუალური ჯანმრთელობის შენარჩუნება მნიშვნელოვან როლს თამაშობს როგორც მოზარდი გოგონების, ასევე, რეპროდუქციული ასაკის ქალების ენდოკრინული ფუნქციის, რეპროდუქციული და ზოგადი ჯანმრთელობისა და სიცოცხლის მაღალი ხარისხის (QOL) შენარჩუნების კუთხით.

მენსტრუალური ციკლის დარღვევები (MCD) კი, რომელთა ეფექტიც არ შემოიფარგლება ქალების მხოლოდ რეპროდუქციული ასაკით და იწვევს ჯანმრთელობის არასასურველი შედეგების განვითარებას რეპროდუქციული ასაკის მიღმაც, მნიშვნელოვნად ზრდის არაგადამდები დაავადებების ტვირთს ზოგადი პოპულაციისთვის მთელს მსოფლიოში. მენსტრუალური ციკლის დარღვევები, მათი შედეგები და, როგორც დიაგნოსტიკისა თუ მკურნალობის, ასევე, სამომავლო პერსპექტივის გამოწვევები, განსხვავდება ქალის ცხოვრების რეპროდუქციული პერიოდების მიხედვით – სხვაობით ასაკში, ენდოკრინულ პროფილში, მოთხოვნასა და რისკებში.

ინტერვენციები: მენსტრუალური ციკლის დარღვევების სამკურნალოდ, უმეტესწილად, სასქესო სტეროიდული ჰორმონალური მედიკამენტები გამოიყენება, როგორც მონოთერაპიის, ასევე კომბინირებული სქემების სახით.

კლინიკური გამოწვევები: სასქესო სტეროიდული მედიკამენტების მოქმედების მთავარ გამოწვევებს ციკლებისა და სისხლდენის კონტროლი, მოქმედება ცენტრალურ ნერვულ სისტემაზე, ურო-გენიტალური და სექსუალური ცვლილებების კონტროლი წარმოადგენს. პაციენტების ნაწილში სასქესო სტეროიდებზე პასუხი პარადოქსულია.

მნიშვნელოვანია თითოეული მათგანის შერჩევის, კომბინირებული გამოყენების შესახებ არჩევანის, მიღების გზისა და დოზირების რეჟიმის, ასევე მიღების ხანგრძლივობის ფრთხილი განსაზღვრა.

მომავლის პერსპექტივა: მენსტრუალური ციკლის დარღვევების (MCD) არსებობის დროს სასქესო სტეროიდული ჰორმონების არჩევასთან დაკავშირებით გადაწყვეტილების მიღებისას, რეკომენდებულია, გავითვალისწინოთ მათი გავლენა სიცოცხლის ზოგად ხარისხზე, გამოვიყენოთ ინდივიდუალიზებული მიდგომა თითოეული პაციენტისთვის, მათ შორის, ფარმაკოგენეტიკური მახასიათებლების, ბიომარკერებისა და ხელოვნური ინტელექტის ინტეგრაცია და მკაფიოდ განვსაზღვროთ თუ რა, როდის და როგორ გამოვიყენოთ სასურველი შედეგების მისაღწევად – გვერდითი ეფექტებისა და გართულებების განვითარების მინიმალიზებული რისკებით.

საკვანძო სიტყვები: მენსტრუალური ციკლის დარღვევები; სასქესო სტეროიდები; ჰორმონალური თერაპია; ენდოკრინული ჯანმრთელობა; ცხოვრების ხარისხი; ინდივიდუალიზებული მკურნალობა

ULTRAFAST WARMING PROTOCOL

LALI KHARABADZE;¹ MARINA KOIAVA²

¹ BSc (Medicine), MSc (Genetics), PhD FellowLead Clinical Embryologist, Clinic Leadermed, Tbilisi, Georgia

² BSc (Biology)Senior Embryologist, Clinic Leadermed, Tbilisi, Georgia

ABSTRACT

Background: Embryo cryopreservation is a crucial aspect of assisted reproductive technologies (ART). The warming process is a critical step that can affect embryo survival and developmental potential. Traditional warming protocols are often labor-intensive and time-consuming.

Objective: To evaluate the efficacy and efficiency of an ultrafast warming protocol for vitrified human blastocysts, compared with conventional multi-step warming methods.

Methods: This pilot study, conducted alongside a literature review, took place in the laboratory of Clinic Leadermed between May 2024 and May 2025. Vitrified human blastocyst-stage embryos were warmed using a single-step solution containing 0.25 M sucrose. Embryos were placed in a pre-heated dish containing 1–4 mL of thawing solution (TS) at 37°C for 1–2 minutes. Embryologic and clinical outcomes were compared with those from conventional multi-step warming protocols.

Results: Ultrafast warming yielded embryologic and clinical outcomes comparable to those of conventional methods. The protocol reduced warming time to approximately 1 minute, improving workflow efficiency by up to 90%. Reduced processing time, enhanced laboratory throughput, and minimized hands-on workload.

Conclusion: The ultrafast warming protocol simplifies the embryo warming process, reduces laboratory time, and maintains high survival and implantation rates. Its efficiency and practicality make it a valuable tool in modern ART laboratories.

Keywords: ultrafast warming, embryo cryopreservation, vitrification, IVF, assisted reproductive technologies

EVALUATING THE LINK BETWEEN MATERNAL VITAMIN D AND ATOPIC DERMATITIS RISK IN OFFSPRING

MARIAM PETRIASHVILI, PhD;¹ LASHA TCHELIDZE, MD;² LIA ZHORZHOLIANI, PhD, Prof.;³ NINO ADAMIA, PhD, Prof.³

¹ K. Chachava Scientific/Research Institute, Tbilisi, Georgia

² Tbilisi State Medical University, Tbilisi, Georgia

³ Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

ABSTRACT

Background: Vitamin D deficiency is considered a worldwide public health problem, particularly because in most countries, large parts of the general population do not meet the dietary vitamin D requirements as recommended by nutritional guidelines. Despite the widespread use of prenatal multivitamin complexes, vitamin D deficiency is common in pregnancy and lactation. Moreover, it was found that 25(OH)D is easily transmitted from mother to fetus and is involved in the process of embryogenesis, ensuring and regulating normal fetal growth and development, the formation of the skeletal system, the proliferation of endothelial cells, lymphocytes, skin and dendritic cells, and controlling the synthesis of certain placental hormones. The studies demonstrated that the prevalence of (AD) was higher in children born to mothers with vitamin D intake during pregnancy.

Methods: A prospective study was conducted in Tbilisi, Georgia. 186 pregnant women and their newborn babies have been examined. Observation of pregnant women was carried out throughout the entire period of pregnancy until delivery, while for newborns, up to 2 years, by providing visits at the ages of 6, 9, 12, and 24 months, respectively. 120 children who developed atopic dermatitis at the age of 2 years were involved in the study population, and 66 children with no clinical signs of atopic dermatitis or allergic family history formed a comparable control group.

Results: 59 mothers (49.2%) of 120 pregnant women whose children developed atopic dermatitis at an early age had an atopic family anamnesis. The average age at disease onset was 11.8 ± 5.5 years. In most cases, atopic dermatitis was accompanied by other allergic reactions, and fathers reported several cases of atopy. The gestational age was significantly different in the reference / compared groups. The early neonatal period passed without any physiological changes; on the fourth-fifth day, all newborns were discharged home. The majority of children

were breastfed (40.0%) or mixed-fed (36.7%). In most cases, the debut of atopic dermatitis was at < 6 months of age (70.8%). According to the results obtained, normal supply of 25(OH)D was fixed in 12.5%, insufficiency in 30%, and deficiency in 57.5% (13.6 ± 4.4 ng/ml) of mothers of children with AD, respectively. Vitamin D (25(OH)D) deficiency during pregnancy prevailed in both cases with hereditary anamnesis of atopy (62.7%) and without it (52.5%), and was reliably more common among the mothers of children with AD compared with control groups. In mothers of children with AD, the summary average value of 25(OH)D was lower (19.7 ± 8.5) than that in the control group (26.3 ± 8.2), indicating a vitamin D deficiency in pregnant women.

Conclusion: The study's conclusion showed that atopic dermatitis in mothers with 25(OH)D deficiency is characterized by a relatively high frequency, early onset, and persistent to moderate course, indicating a connection between vitamin D deficiency in pregnant women and the clinical features of atopic dermatitis (AD) in children. Detecting vitamin D levels in pregnant women can be applied as predictive criteria for the interpretation of the formation, progression, and severity of atopic dermatitis. According to those mentioned above, a wide-scale study regarding the correction of vitamin D deficiency in pregnant women can be considered.

Keywords: vitamin D deficiency; atopic dermatitis; pregnancy; 25(OH)D; fetal immune development; maternal health

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INFECTION-INDUCED CAPACITATION DISRUPTION: THE ROLE OF TRICHOMONAS VAGINALIS IN PREECLAMPSIA AND FETAL GROWTH RESTRICTION

**LASHA TCHELIDZE;¹ NINO KHARADZE;² NINO KHVITIA;¹
EKATERINE MCHEDLISHVILI;¹ MANANA PRUIDZE;¹ NATALIA TCHILADZE;²
NINO ADAMIA;³ NIKOLOZ SAGHIRASHVILI¹**

¹ Department of Medical Biology and Parasitology, Tbilisi State Medical University, Tbilisi, Georgia

² Assistant Professor, Department of Medical Biology and Parasitology, Tbilisi State Medical University, Tbilisi, Georgia

³ Department of Pediatrics, Tbilisi State Medical University, Tbilisi, Georgia

ABSTRACT

Background: Trichomonosis is a dangerous sexually transmitted illness caused by *Trichomonas vaginalis*, a parasitic protozoan. Trichomoniasis has been associated with numerous perinatal problems, male and female genitourinary tract infections, and an increased risk of HIV transmission, which largely affects the process of capacity. Premature birth has been linked to the *T. vaginalis*, which was previously considered a “minor” one. A large multicenter investigation found that disorders were related to rupture of the premature membrane and low-weight birth after controlling for demographic, behavioral, and microbiological factors. According to Kissinger (2018), trichomoniasis is strongly linked to early labor and delivery. In Georgia, the exact prevalence of this disease is unknown.

Methods: We studied different articles related to this topic. The main sources were PubMed and the National Institutes of Health (NIH). We investigated the medical information of 48 patients with *Trichomonas vaginalis* and 48 healthy patients.

Results: We confirmed that pregnancy-related preeclampsia was more common in *T. vaginalis*-infected women than in non-infected women. There was a correlation between *T. vaginalis* and preterm birth and low birth weight in another research on adolescent mothers. Veterinary research suggests that *Trichomonas* infections may contribute to pregnancy complications. For bovine trichomonas-infected cattle, immunization with *Trichomonas* has been shown to reduce abortion rates. Preterm labor and colonization or infection of the lower gastrointestinal tract during pregnancy are not known to be associated specifically in pregnancy. The majority view holds that infection triggers the production of local cytokines, which in turn trigger the

onset of labor. Infections of the lower genital tract in pregnant women have been linked to vaginal fluid. As a result of parasite-induced inflammation, many African studies have found a link between HIV and trichomoniasis. The prevalence of trichomoniasis in Rwandan pregnant women with and without HIV infection was considerably different from that in women without HIV infection. A multivariate analysis conducted on a Zairean cohort of women by Crouch et al., (2018) indicated trichomoniasis to be a significant risk factor for HIV infection (odds ratio, 1.9). Transmission of HIV is increased when *T. vaginalis* is co-infected. According to a Malawian study, males with trichomoniasis had significantly higher median HIV RNA concentrations in their seminal fluid than those with symptoms of unexplained urethritis. Anti-HIV medication decreases the HIV RNA levels in the body to the same level as in healthy people (Tine et al., 2019).

Conclusion: *T. vaginalis* has a complicated pathogenesis, according to the study, with components such as hemolysis and cell-detachment factor, as well as adhesion and hemolysis, all contributing to the disease's pathogenesis. The ability of *T. vaginalis* to adapt to its continually changing environment is related to its close association with the indigenous vaginal flora, its advanced immune evasion mechanisms, and its unique stress responses. The research aimed to investigate the impact of *Trichomonas vaginalis* on the process of Capacitas. *Trichomonas* infection is prevalent and has been associated with many public health problems, including an increase in HIV transmission. Metronidazole is a safe and efficient treatment choice; however, resistant strains are becoming more prevalent. The immunology, pregnancy hazards, appropriate diagnosis, and public health control of this sickness remain unknown.

Keywords: trichomonas vaginalis; preeclampsia; fetal growth restriction; HIV co-infection; pregnancy complications; sexually transmitted infections; metronidazole resistance

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PREGNANCY OUTCOME AFTER TRANSFERRING GENETICALLY TESTED EMBRYOS VS. NON-TESTED EMBRYOS

TEA CHARKVIANI, MD;^{1,2} JENARO KRISTESASHVILI, MD, PhD;¹ TENGIZ ZHORZHOLADZE, MD;³ NINO KUTCHUKHIDZE, PhD;³ TAMAR BARBAKADZE, MD, PhD;² MARIAM GABADZE, MD;² TAMAR KBILASHVILI, MD;² MARIAM MAKHARADZE⁴

¹ Faculty of Clinical and Translational Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia

² Department of Reproductive Endocrinology, Georgian-American Center for Reproductive Medicine "ReproART", Tbilisi, Georgia

³ Department of Embryology, Georgian-American Center for Reproductive Medicine "ReproART", Tbilisi, Georgia

⁴ Undergraduate, David Tvildiani Medical University, Tbilisi, Georgia

ABSTRACT

Background: Assisted reproductive technology (ART) has transformed fertility treatment, providing opportunities for many couples who otherwise would face difficulty conceiving. A critical factor in ART success is the selection of viable embryos. Preimplantation genetic testing for aneuploidy (PGT-A) has emerged as a widely used method to improve embryo selection, enhance pregnancy outcomes, and reduce the risk of miscarriage.

Aim: To compare pregnancy outcomes between genetically tested (PGT-A) and non-tested embryos to assess the clinical value of PGT-A in optimizing ART outcomes.

Materials and Methods: A retrospective comparative study included 225 patients under 35 years of age, including recipients, patients of advanced maternal age, and those with recurrent miscarriage. All underwent ovarian stimulation with a GnRH-antagonist protocol. Blastocysts in the PGT-A group were tested using next-generation sequencing (NGS). Outcomes included biochemical pregnancy, miscarriage, and live birth.

Results: In the PGT-A group (n=110), 116 embryos were transferred. Fifty-nine pregnancies (53.6%) were achieved; 4 miscarriages (6.8%) and two biochemical pregnancies (3.4%) occurred. In total, 53 pregnancies continued to delivery (89.8% of pregnancies, 48.2% of all transfers). In the non-PGT-A group (n=115), 220 embryos were transferred, resulting in 41 pregnancies (35.7%). Of these, seven miscarried at 6 weeks (17.1%), 2 miscarried at 14–16 weeks (4.9%), and one fetus (2.4%) had a chromosomal abnormality. Thirty-two patients delivered healthy babies (78% of pregnancies, 27.8% of transfers).

Conclusion: PGT-A significantly improves pregnancy outcomes and reduces miscarriage rates by enabling the selection of euploid embryos. Its use should, however, be tailored to patient-specific factors. Larger prospective studies are needed to refine patient selection criteria.

Keywords: Preimplantation genetic testing (PGT); next-generation sequencing (NGS); in vitro fertilization (IVF); implantation rate; miscarriage rate; live birth rate; assisted reproductive technology (ART)

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Introduction

Assisted reproductive technologies (ARTs) have become a cornerstone of modern reproductive health care, offering solutions to many women and couples facing fertility challenges. As the field continues to evolve, enhancing the effectiveness of ARTs remains a priority. The success of ART treatments is influenced by various factors, including egg quality associated with the woman's age,⁵⁻⁶ the protocols of controlled ovarian stimulation (COS)⁷⁻⁸, the type of ovulation trigger administered for final oocyte maturation, blastocyst quality and ploidy,⁹⁻¹⁰ endometrial condition, and overall health. Moreover, synchronization between the endometrium and embryo is critical during implantation to maximize the chances of a successful pregnancy. One significant advancement in ART is the development of preimplantation genetic testing (PGT), which has revolutionized in vitro fertilization (IVF). By enabling the identification of chromosomally normal embryos before transfer, PGT reduces the risk of implantation failure and miscarriage, thus improving pregnancy outcomes.¹¹

Among the various forms of PGT, preimplantation genetic testing for aneuploidy (PGT-A) has become widely utilized to enhance embryo selection.¹ PGT-A is used to improve pregnancy outcomes and reduce the risk of miscarriage. It aims to identify embryos with the correct chromosomal complement (euploid embryos) and avoid transferring aneuploid embryos, which are more likely to result in failed implantation or miscarriage.² The primary goal of PGT-A is to increase implantation rates by ensuring that only euploid embryos are transferred, thereby improving the efficiency of IVF cycles.³

Historically, embryo selection was based solely on morphological assessment, a method that, while useful, has limitations in detecting chromosomal abnormalities that could negatively impact pregnancy viability.¹² The introduction of genetic screening techniques such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), and next-generation sequencing (NGS) has significantly improved the accuracy of embryo assess-

ment⁴. These technologies allow for a more precise distinction between euploid, aneuploid, and mosaic embryos, thereby refining the embryo selection process.¹³

Despite the clear advantages of PGT-A in reducing implantation failure and pregnancy loss, the routine use of this technology remains a subject of debate.¹⁴ Critics argue that PGT-A may not constantly improve cumulative live birth rates, especially in younger women with a good ovarian reserve, as some aneuploid embryos have been shown to self-correct after implantation.¹⁵ Additionally, the cost of PGT-A adds a financial burden to an already expensive IVF process, raising questions about its cost-effectiveness.²

This article aims to provide a comprehensive comparison of pregnancy outcomes between genetically tested and non-tested embryos by examining key factors such as implantation rates, miscarriage rates, live birth rates, and time to pregnancy to determine the clinical value of PGT-A and its role in optimizing ART outcomes.¹¹

Materials and Methods

Study Design and Participants

This retrospective study was conducted at the Georgian-American Center for Reproduction Medicine, ReproART, from January 2019 to March 2021. A total of 225 patients under the age of 35 were included. The study population also included egg donors for patients of advanced maternal age, as well as younger patients with a history of multiple miscarriages.

Inclusion and Exclusion Criteria

Patients were selected based on standardized criteria. The inclusion criteria are presented in Table 1.

Exclusion criteria included the following:

- Irregular menstrual cycles
- Abnormal body mass index (BMI)
- Polycystic ovary syndrome (PCOS)
- Sexually transmitted infections (STIs)
- Complicated obstetric history
- Endometriosis
- Uterine abnormalities
- Previous ovarian surgeries
- Male factor infertility

Ovarian Stimulation Protocol

All participants underwent ovarian stimulation using a GnRH-antagonist protocol, with prior ovarian downregulation via oral contraceptives to synchronize donor and recipient cycles. Stimulation was initiated on the fifth day after discontinuing oral contraceptives using recombinant FSH (Gonal-F, Merck Serono, Germany) in combination with highly purified human menopausal gonadotropin (hMG; Menopur, Ferring Pharmaceuticals, Switzerland).

The initial gonadotropin dose was 450 IU of FSH for the first two days, followed by dose adjustments based on ultrasound monitoring and hormonal evaluations (FSH, LH, E₂). The average stimulation duration was 11–12 days (parameters described in Table 2).

When at least one follicle reached 14 mm in diameter, Cetrotide 0.25 mg (Merck Serono, Germany) was administered. Ovulation triggering included one of the following:

- 10,000 IU hCG (Pregnyl, Organon, Netherlands)
- 1,500 IU hCG + GnRH-agonist (Decapeptyl 0.2 mg, Ferring Pharmaceuticals, Switzerland)
- GnRH-agonist alone (Decapeptyl 0.2 mg) for patients with >25 follicles

Oocyte Retrieval and Fertilization

Oocyte retrieval was performed 35 hours after ovulation trigger using transvaginal ultrasound-guided aspiration (17-gauge needles, Gynetics-Fertitech, Belgium) at 120 mmHg aspiration pressure under IV anesthesia.

All retrieved oocytes underwent intracytoplasmic sperm injection (ICSI), and fertilization assessment was conducted 16–18 hours post-ICSI.

Embryo Culture and PGT-A Testing

Embryos were cultured using Quinn's Advantage media (Origio, Netherlands). Blastocyst formation was assessed on days 5, 6, and 7 using Gardner's grading method¹⁶. Trophectoderm biopsy was performed for PGT-A testing at Reprogenetics/Cooper Genomics (New Jersey, USA, or UK) using next-generation sequencing (NGS).

Embryo Transfer and Endometrial Preparation

Endometrial preparation for embryo transfer involved 9 mg of estradiol daily, with additional GnRH-agonist suppression for surrogate mothers. Progesterone (Luteina 200 mg vaginally and Prolutex 25 mg intramuscularly) was initiated when endometrial thickness exceeded 8 mm.

Retrospective Analysis

A retrospective analysis was conducted to compare pregnancy outcomes between PGT-A–tested and non-tested embryos.

Analytical Approach and Statistical Methods

All statistical analyses and visualizations were performed using t-tests, ANOVA, and Python to determine the significance of differences between groups.

Results and Discussion

A total of 225 patients underwent frozen embryo transfer (FET) and were divided into two groups: the PGT-A group included 110 patients, and the non-PGT-A group included 115 patients. A total of 116 embryos were transferred in the PGT-A group; single embryos were transferred to 104 patients, and **six** patients requested the transfer of **2** blastocysts. This resulted in 59 pregnancies (53.6%), of which four pregnancies miscarried at 6 to 7 weeks of gestation (6.8%), two biochemical pregnancies occurred (3.4%), and 53 pregnancies continued to delivery (89.8% of pregnancies, 48.2% of all transfers), with live births occurring at 38 to 40 weeks of gestation.

In the non-PGT-A group, 220 embryos were transferred (1.91 embryos per patient), leading to 41 pregnancies (35.7%). Of these, seven pregnancies miscarried at 6 weeks (17.1%); 2 patients experienced late miscarriage at 14 to 16 weeks (4.9%); and one fetus out of those 2 (2.4%) was diagnosed with a chromosomal abnormality. Thirty-two patients delivered healthy babies at 37 to 40 weeks of gestation (78% of pregnancies, 27.8% of all transfers). The comparison of pregnancy outcomes is shown in Figure 1.

To rigorously test whether the difference in pregnancy rates between the PGT-A and non-PGT-A groups was statistically significant, a logistic regression analysis (Figure 2) was performed. The results revealed a statistically significant difference between the PGT-A and non-PGT-A groups ($P < 0.001$). The Z value (-2.18) confirmed the distinct outcomes in the PGT-A group after adjusting for group size. The ROC curve demonstrated the model's strong predictive accuracy, with an AUC of 0.90, highlighting its effectiveness in distinguishing between the two groups regarding pregnancy outcomes.

The findings of this study support the efficacy of PGT-A in improving pregnancy outcomes by increasing implantation rates, reducing miscarriage rates, and optimizing embryo selection. The pregnancy rate in the PGT-A group (53.6%) was significantly higher than in the non-PGT-A group (35.7%), demonstrating the advantage of selecting euploid embryos. Furthermore, the miscarriage rate was lower in the PGT-A group (6.8%) compared with the non-PGT-A group (17.1%), emphasizing the role of genetic testing in reducing early pregnancy losses.

Numerous studies have compared the efficacy of PGT-A with non-PGT-A embryo transfers, with mixed results depending on the patient population and study design. PGT-A is consistently associated with higher implantation and clinical pregnancy rates, particularly in older women and those with recurrent pregnancy loss. For instance, clinical pregnancy rates after PGT-A have been reported to reach approximately 60%, significantly higher than non-PGT-A transfers.¹⁷ Similarly, Scott et al demonstrated that PGT-A cycles resulted in an implantation rate of approximately 65%, further highlighting the technique's potential to improve pregnancy outcomes in select populations.

One of the key advantages of PGT-A is its ability to reduce miscarriage rates by selecting euploid embryos, which have a lower likelihood of resulting in early pregnancy loss. Studies such as Dahdouh et al found that miscarriage rates after PGT-A were significantly lower, often below 10%, compared with non-PGT-A transfers.¹⁸

However, despite these advantages, the universal application of PGT-A remains controversial. Some studies, such as Mastenbroek et al, found no significant difference in live birth rates between PGT-A and non-PGT-A groups in younger women, raising concerns about the necessity of genetic testing in patients with a good prognosis.¹⁹ These findings suggest that PGT-A should be applied selectively rather than routinely, particularly in younger patients with high-quality embryos.

In addition to these clinical considerations, the cost-effectiveness of PGT-A has become an essential factor in evaluating its broader application in IVF treatments. While the total cost of an IVF cycle that includes PGT-A is higher than that of a conventional IVF cycle without genetic testing, the cost-effectiveness of PGT-A becomes evident when considering long-term outcomes. Transferring non-PGT-A embryos is associated with lower implantation rates, higher miscarriage risks, and increased emotional and financial burdens on patients.²⁰

Patients undergoing IVF without genetic testing may require multiple embryo transfers because of failed implantations, ultimately leading to increased expenses over time. Studies have shown that for specific age groups, PGT-A can reduce the average cost per infant, making it a cost-effective strategy in particular populations.²¹

Failed implantation and miscarriage result in psychological distress and emotional strain, prolonging the journey to parenthood. Research indicates that infertility and repeated IVF failures can lead to increased rates of depression and anxiety among patients.²² The physical and psychological stress of repeated miscarriages can also place couples at risk of relationship strain.

Recurrent pregnancy loss has been associated with significant psychological distress for both partners, potentially leading to symptoms of depression, anxiety, and lowered self-esteem. Additionally, the emotional toll of recurrent miscarriages can negatively impact couples' relationships and sexual intimacy.²³

In cases where a non-PGT-A embryo results in pregnancy but later leads to miscarriage, medical interventions such as dilation and curettage (D&C) may be necessary, which can pose risks to the patient's reproductive health and reduce future pregnancy success rates. For instance, a study published in *Human Reproduction* found that a history of curettage is associated with an increased risk of preterm birth in subsequent pregnancies. However, other research indicates that D&C does not significantly affect future pregnancy outcomes.²⁴

Overall, this study supports the use of PGT-A as an effective tool for improving pregnancy outcomes, particularly in women at risk of implantation failure or miscarriage. However, its clinical application should be tailored based on individual patient characteristics, ovarian reserve, and clinical history to maximize the chances of a successful pregnancy. Further large-scale studies are needed to refine the indications for PGT-A and confirm its long-term benefits in diverse patient populations.

Understanding these differences is crucial for both reproductive specialists and patients in making informed decisions regarding the use of genetic testing in IVF cycles.¹³

Conclusion

PGT-A offers a significant advantage in improving pregnancy outcomes by selecting euploid embryos and reducing miscarriage rates. However, its routine use should be individualized and tailored to patient-specific factors. Further large-scale studies are needed to optimize patient selection criteria for PGT-A, ensuring its application is both cost-effective and beneficial for intended parents.

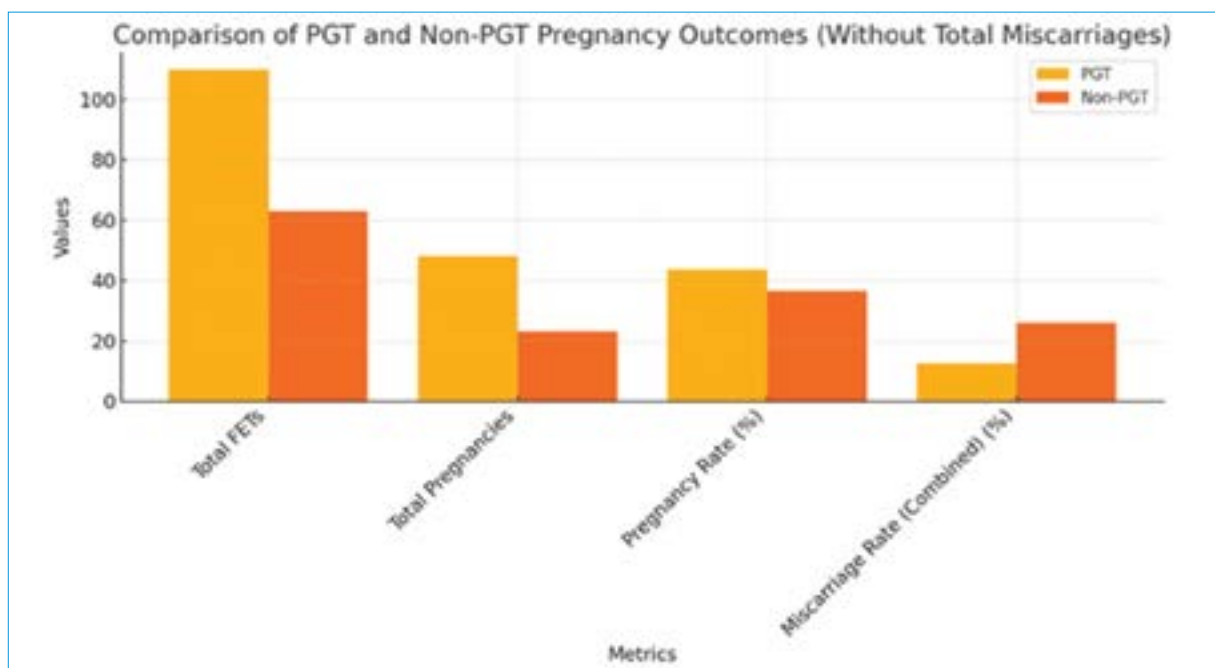


Figure 1. Graphical comparison of pregnancy outcomes following transfer of genetically tested (PGT-A) and non-tested embryos. Pregnancy rates were higher and miscarriage rates were lower in the PGT-A group.

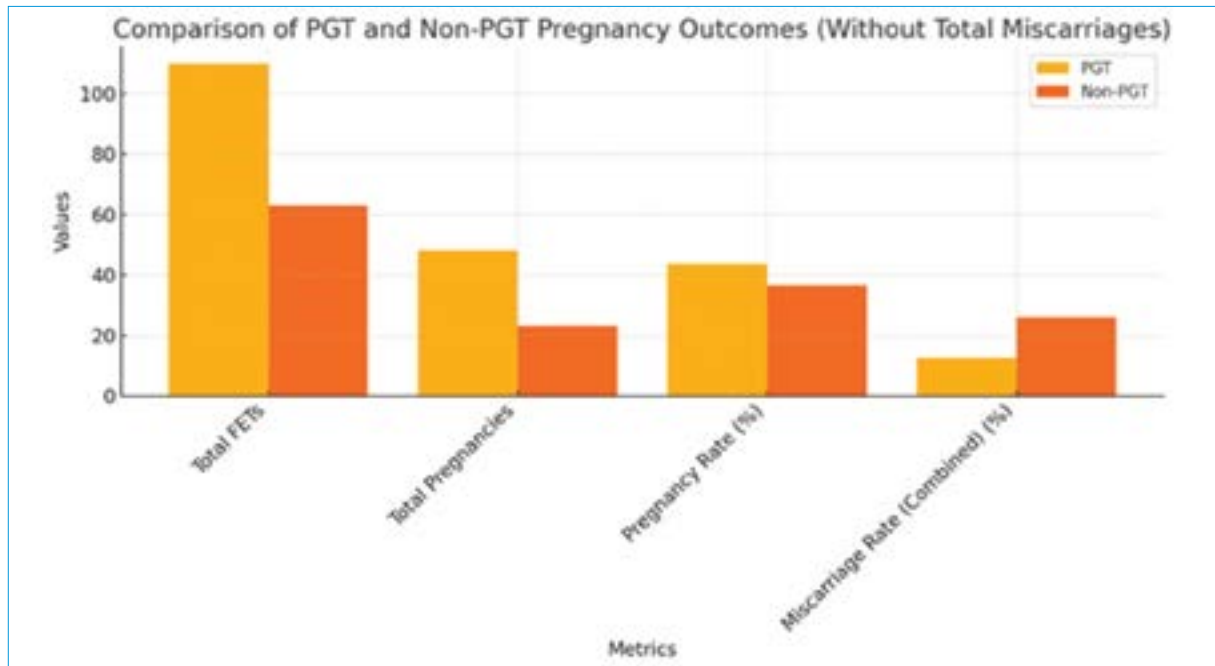


Figure 2. Receiver operating characteristic (ROC) curve analysis comparing pregnancy outcomes between genetically tested (PGT-A) and non-tested embryo transfers. Logistic regression analysis revealed a statistically significant difference between the two groups, with an area under the curve (AUC) of 0.90, indicating strong predictive accuracy for distinguishing pregnancy outcomes based on embryo genetic testing.

Table 1. Patient Inclusion Criteria and Average Indicators

Parameter	Average Value
Age	25.0 – 35 years
AMH (ng/mL)	4.2 ± 2.0
Antral Follicle Count (AFC)	24.7 ± 7.6
BMI	21.9 ± 2.4
Follicle-Stimulating Hormone (FSH) (mIU/mL)	7.8 ± 2.1
Thyroid-Stimulating Hormone (TSH) (mIU/mL)	2.2 ± 1.3
Prolactin (PRL) (ng/mL)	16.3 ± 5.7
Sperm Parameters	Normal

Table 2. Ovarian Stimulation Parameters

Parameter	Mean Value ± SD
FSH Level at Downregulation (mIU/mL)	3a.6 ± 2.5
Estradiol (E2) Level at Downregulation (pg/mL)	10.4 ± 8.6
Total Gonadotropins Administered (IU)	3203 ± 536
Stimulation Duration (Days)	10.5 ± 2.1
E2 Level on Trigger Day (pg/mL)	7325 ± 1567
Follicle Diameter at Retrieval (mm)	18.4 ± 1.7
Total Retrieved Oocytes	± 5.5

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CORRECTION OF UTERINE MICROFLORA COMPOSITION DISORDERS AND EMBRYO TRANSFER TIMING IN PATIENTS WITH RECURRENT IMPLANTATION FAILURE: CLINICAL EFFECTS AND PROGNOSTIC FACTORS

NATO SHAMUGIA, *Cand. Sci. (Med.), Assoc. Prof.*; ^{1,3}

POLINA VARLAKOVA, *Senior Laboratory Assistant*; ^{1,3}

NATALIA PODZOLKOVA, *Dr. Sci. (Med.), Prof.*; ^{1,2}

¹ *Russian Medical Academy of Continuous Professional Education, Ministry of Healthcare of the Russian Federation, Moscow, Russia*

² *State Clinical Hospital named after S.P. Botkin, Department of Health of Moscow, Moscow, Russia*

³ *GMS IVF Clinic, Moscow, Russia*

ABSTRACT

Background: Recurrent implantation failure (RIF) represents a serious challenge in reproductive medicine, limiting the effectiveness of assisted reproductive technology (ART) programs. Contemporary research demonstrates the pivotal role of endometrial microbiome and receptivity disorders in the pathogenesis of implantation failure, substantiating the need for comprehensive diagnosis of maternal factors.

Objective: To evaluate the effectiveness of an individualized approach to correcting endometrial microbial imbalance and optimizing embryo transfer timing in women with recurrent implantation failure.

Materials and Methods: A prospective controlled study of 107 patients with RIF undergoing vitrified embryo transfer was conducted. Participants were stratified into a study group (n=54) with molecular genetic ERA and EMMA testing (Igenomix, Spain) followed by personalized therapy, and a control group (n=53) with standard protocol. Implantation rates, clinical pregnancy rates, and live birth rates were analyzed. Multivariate analysis of endometrial disorder predictors was performed.

Results: Molecular genetic testing revealed a displaced implantation window in 51.85% of study group patients; microbial imbalance with *Lactobacillus* spp. deficiency was registered in 74.08% of subjects. The study group achieved significantly higher efficacy parameters regardless of preimplantation genetic screening application ($p < 0.05$). Statistically significant associations were established between invasive intrauterine procedures and dysbiosis development ($p = 0.0053$), as well as between chronic endometritis and receptivity impairment ($p = 0.006$).

Conclusions: Integrated assessment of endometrial microbiome and functional status with subsequent targeted correction demonstrates significant improvement in ART outcomes in patients with RIF. Molecular genetic diagnostic methods should be appropriately included in the examination algorithm for this patient category.

Keywords: recurrent implantation failure; endometrial microbiome; implantation window; personalized medicine

Introduction

Blastocyst implantation represents a critical stage of the reproductive process, requiring precise synchronization between the developing embryo and functionally prepared endometrium. Despite substantial progress in assisted reproductive technologies, including improved ovarian stimulation protocols, optimized culture conditions, and implementation of preimplantation genetic screening, the problem of recurrent implantation failure (RIF) remains one of the most challenging aspects of modern reproductive medicine.

Diagnostic criteria for RIF vary between different medical societies. According to the updated clinical guidelines of the Russian Ministry of Health for female infertility management (2024), RIF diagnosis is justified when two or more unsuccessful transfers of quality embryos occur [1]. The European Society of Human Reproduction and Embryology (ESHRE) in its latest guideline revision (2023) proposes a differentiated approach considering patient age and embryo genetic testing status, establishing threshold values from two to six unsuccessful attempts depending on the clinical situation [2].

The etiopathogenesis of RIF is characterized by multifactoriality, including embryonic, maternal, and procedural aspects. Contemporary research pays particular attention to endometrial factors, which, according to various estimates, account for 18-27% of implantation failure cases [3]. Among these, endometrial microbiome disorders and dysregulation of uterine mucosa receptivity acquire primary importance.

The objective of this study was to comprehensively evaluate the effectiveness of a personalized approach to diagnosing and correcting endometrial disorders in patients with RIF using modern molecular genetic methods.

Materials and Methods

The study was conducted at the reproductive medicine center “GMS IVF” with scientific and methodological support from the Department of Obstetrics and Gynecology of the “Russian Medical Academy of Continuous Professional Education” of the Russian Ministry of Health. The study design represented a prospective controlled observation conducted from October 2021 to November 2024.

The study included women of reproductive age (18-40 years) with verified RIF diagnosis according to Russian Ministry of Health criteria, planning cryopreserved embryo transfer programs in hormone replacement therapy (HRT) cycles. Additional inclusion criteria were: endometrial thickness on transfer day ≥ 7 mm, body mass index < 30 kg/m², and absence of acute pelvic inflammatory disease [4].

Exclusion criteria included: age > 40 years, decompensated somatic pathology, anatomical uterine cavity anomalies (submucous myoma, intracavitary polyps, synechiae, active hydrosalpinx), uncontrolled endocrine disorders, as well as refusal to participate in the study or protocol non-compliance.

The final sample comprised 107 patients who were stratified into two groups using sequential allocation. The study group (n=54) included women who underwent extended endometrial examination with subsequent personalized transfer preparation. The control group (n=53) received standard therapy without additional testing. For in-depth analysis, each group was further divided into subgroups depending on preimplantation genetic testing for aneuploidy (PGT-A) application (Figure 1).

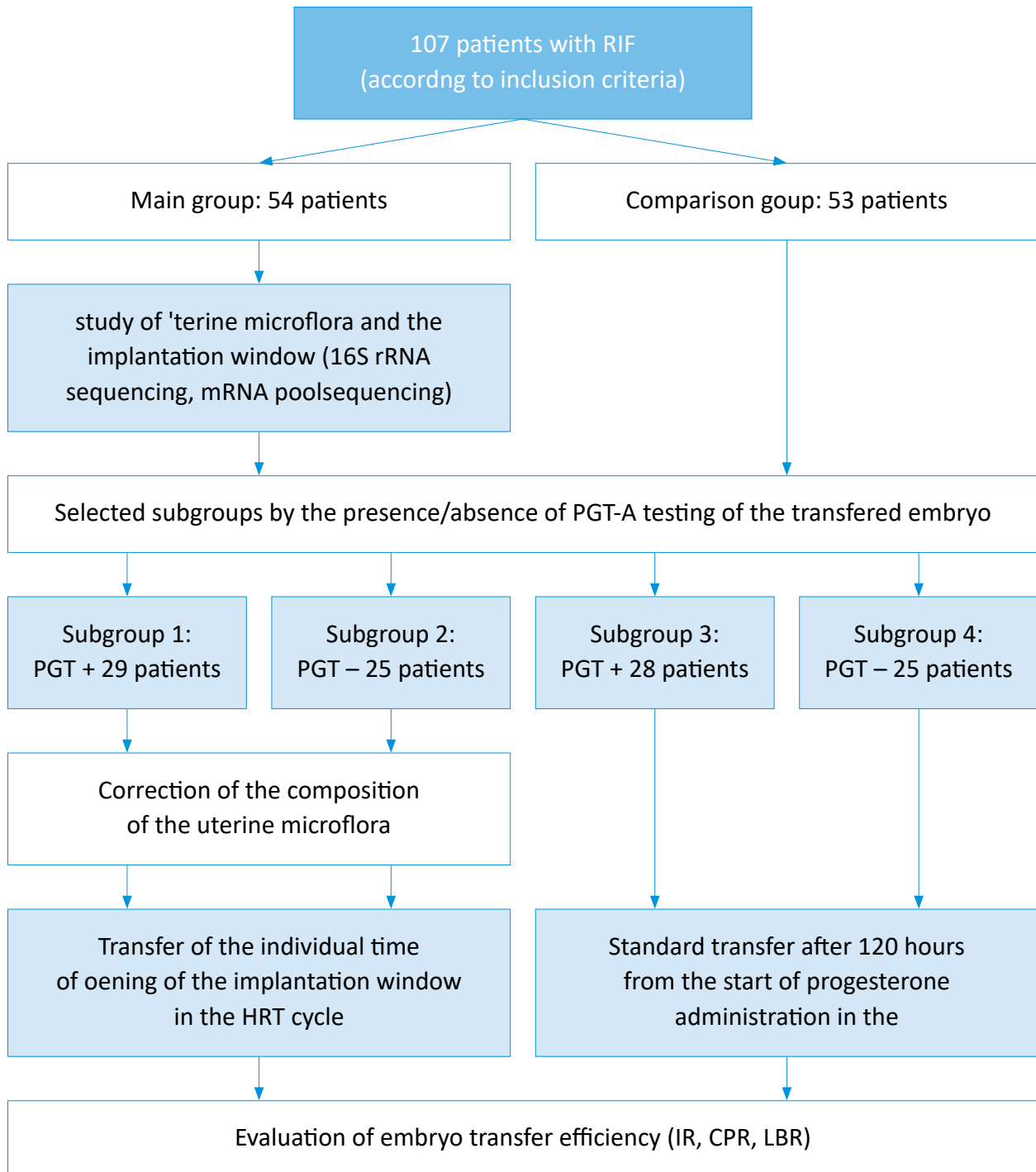


Figure 1. Study design schema

All participants underwent standardized preconception examination according to Russian Ministry of Health Order No. 803n [4]. The HRT protocol included estradiol valerate 6 mg/day orally with subsequent addition of micronized progesterone 600 mg/day intravaginally.

In the study group, a Pipelle endometrial biopsy was performed at 120 hours from progesterone support initiation with strict aseptic requirements. The obtained biomaterial underwent molecular genetic analysis using ERA (Endometrial Receptivity Analysis) tests for receptivity assessment and EMMA (Endometrial Microbiome Metagenomic Analysis) for microbial composition characterization (Igenomix, Spain).

Based on ERA testing results, the endometrium was classified as:

- Pre-receptive (requiring progesterone exposure prolongation by 24-48 hours)
- Early receptive (extension by 12 hours)
- Receptive (standard transfer timing)
- Late receptive (reduction by 12 hours)
- Post-receptive (reduction by 24-48 hours)

When microbial imbalance was detected by EMMA analysis, targeted correction was performed according to a developed algorithm [5]. The type of identified disorders determined treatment strategy: when conditionally pathogenic flora dominated, targeted antibacterial agents were used, followed by lactobacillary pool restoration; with moderate changes, treatment was limited to probiotic therapy with preparations containing *Lactobacillus* spp. strains. In the study group, embryo transfer was performed at strictly personalized times according to the identified implantation window. The control group used a standard protocol with transfer at 120 hours after progesterone support initiation.

Study Endpoints

Primary endpoints included: implantation rate (IR), determined by β -hCG dynamics in the 10-1000 mIU/ml range; clinical pregnancy rate (CPR), confirmed by ultrasound visualization of gestational sac and embryonic cardiac activity; live birth rate (LBR), representing birth of a viable infant.

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics v.26 (IBM, USA) and JMP Pro 17 (SAS, USA) software. Distribution normality was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. Quantitative variables are presented as median [25th; 75th percentiles] for non-parametric data. Absolute and relative frequencies describe categorical variables.

Intergroup comparisons of quantitative indicators were performed using the Mann-Whitney U test, categorical variables using Pearson's χ^2 test or Fisher's exact test for expected frequencies <5. Logistic regression analysis was used to identify risk factors with the calculation of odds ratios (OR) and 95% confidence intervals (CI). The critical significance level was set at $p < 0.05$.

Results

Comparative analysis of baseline characteristics revealed no statistically significant differences between groups in age, anthropometric parameters, infertility duration, number of previous ART attempts, and endometrial morphometric indicators ($p > 0.05$ for all comparisons), confirming group comparability and randomization validity.

Endometrial Microbiome Characteristics

Metagenomic analysis of the endometrial microbiome in study group patients demonstrated significant heterogeneity of microbial communities. Normobiosis with *Lactobacillus* spp. dominance (>90% of total microbial mass) was established in only 14 patients (25.92%). Various dysbiotic disorder variants were identified in 40 women (74.08%), including moderate lactobacilli reduction in 14 (25.92%), pronounced dysbiosis in 8 (14.81%), and critical microflora depletion in 18 (33.33%) subjects (Figure 2).

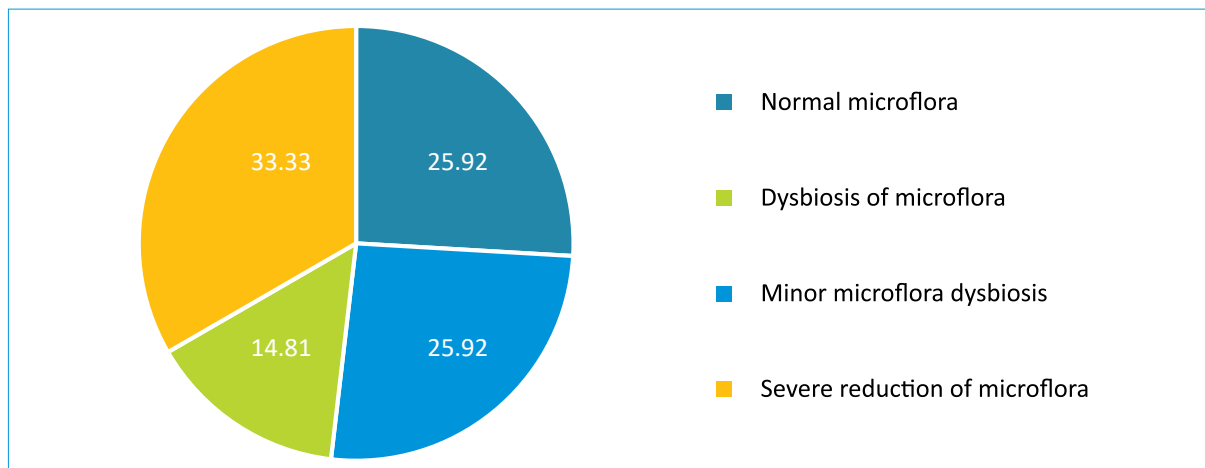


Figure 2. Distribution of endometrial microbiome types in patients with RIF.

Detailed taxonomic analysis showed a median lactobacilli proportion of 82.66% [53.65; 94.82], substantially below the normative threshold. Among conditionally pathogenic microorganisms, *Gardnerella* (52.95% [29.24; 58.28]), *Streptococcus* (30.03% [19.60; 40.47]), and *Propionibacterium* (15.21% [12.87; 20.03]) had the greatest representation.

Endometrial Receptivity Assessment

Molecular genetic receptivity testing revealed implantation window displacement in 28 of 54 study group patients (51.85%). The most frequent variant was pre-receptive status, registered in 18 women (33.33%), indicating the need for progesterone exposure prolongation. Early receptive type was determined in 6 patients (11.11%), late receptive in 3 (5.55%), and post-receptive in 1 (1.85%). Receptive status at standard times was recorded in 26 women (48.15%) (Figure 3).

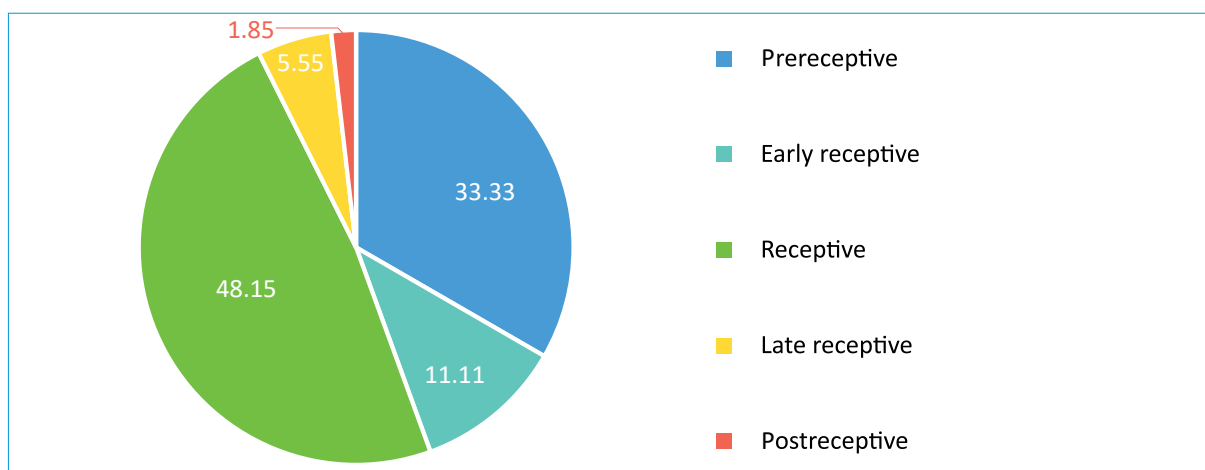


Figure 3. Distribution of endometrial receptivity types according to ERA testing.

Temporal parameters of implantation window opening were characterized by significant variability: from 96 to 168 hours of progesterone exposure with a median of 120 hours [119.25; 140.0], emphasizing the need for an individualized approach.

Analysis of Endometrial Disorder Predictors

Logistic regression analysis revealed statistically significant associations between clinical-anamnestic factors and endometrial disorder development. The strongest predictors of microbial imbalance were invasive intrauterine interventions in history (OR=6.346; 95% CI: 1.732-23.256; $p=0.0053$) and chronic endometritis (OR=7.360; 95% CI: 2.111-25.659; $p=0.0017$).

Endometrial receptivity impairment demonstrated a significant association with chronic endometritis in history (OR=5.600; 95% CI: 1.638-19.148; $p=0.006$), indicating the pathogenetic role of chronic inflammation in dysregulation of molecular mechanisms of endometrial preparation for implantation.

Personalized Approach Effectiveness

In patients with euploid embryos (PGT-A subgroups), the personalized strategy demonstrated significant advantages: IR in the study group was 79.31% versus 53.57% in the control ($p=0.0393$); CPR was 79.31% versus 46.43% ($p=0.0101$); LBR was 72.41% versus 46.43% ($p=0.0456$), respectively (Chart 1).

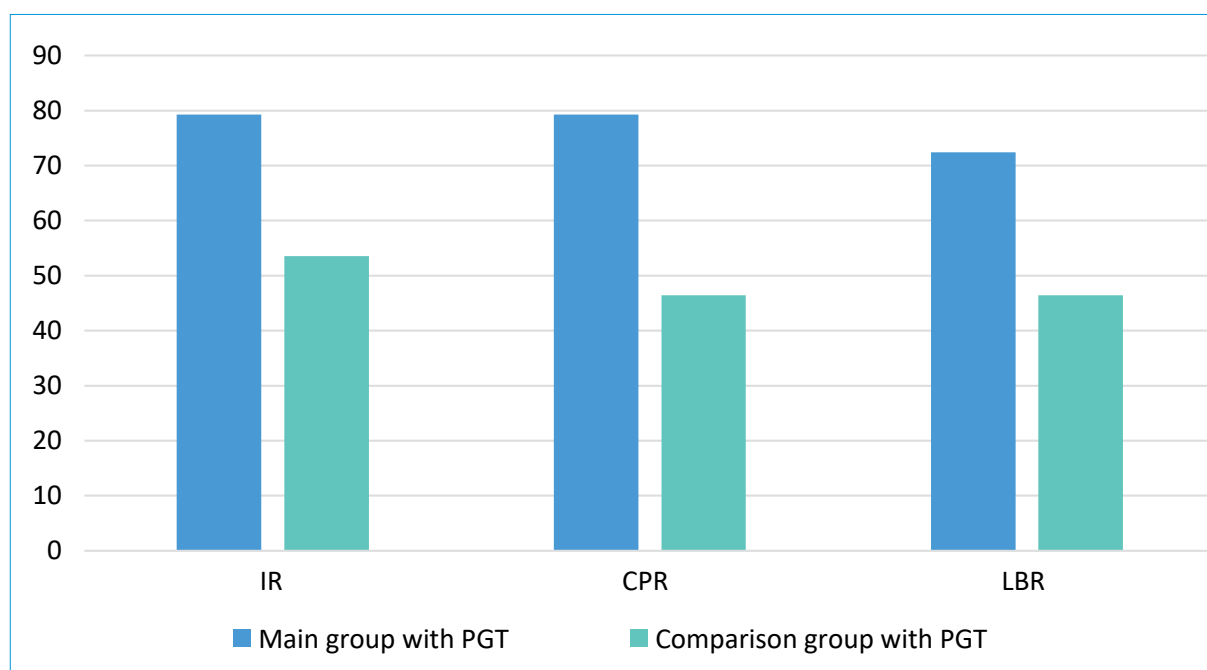


Chart 1. Comparative effectiveness in patients with euploid embryo transfer.

Similar trends were observed in subgroups without PGT-A: IR increased from 40% to 68% ($p=0.047$), CPR from 32% to 60% ($p=0.047$), LBR from 28% to 56% ($p=0.0449$), demonstrating the universality of the personalized approach regardless of embryo genetic status (Chart 2).

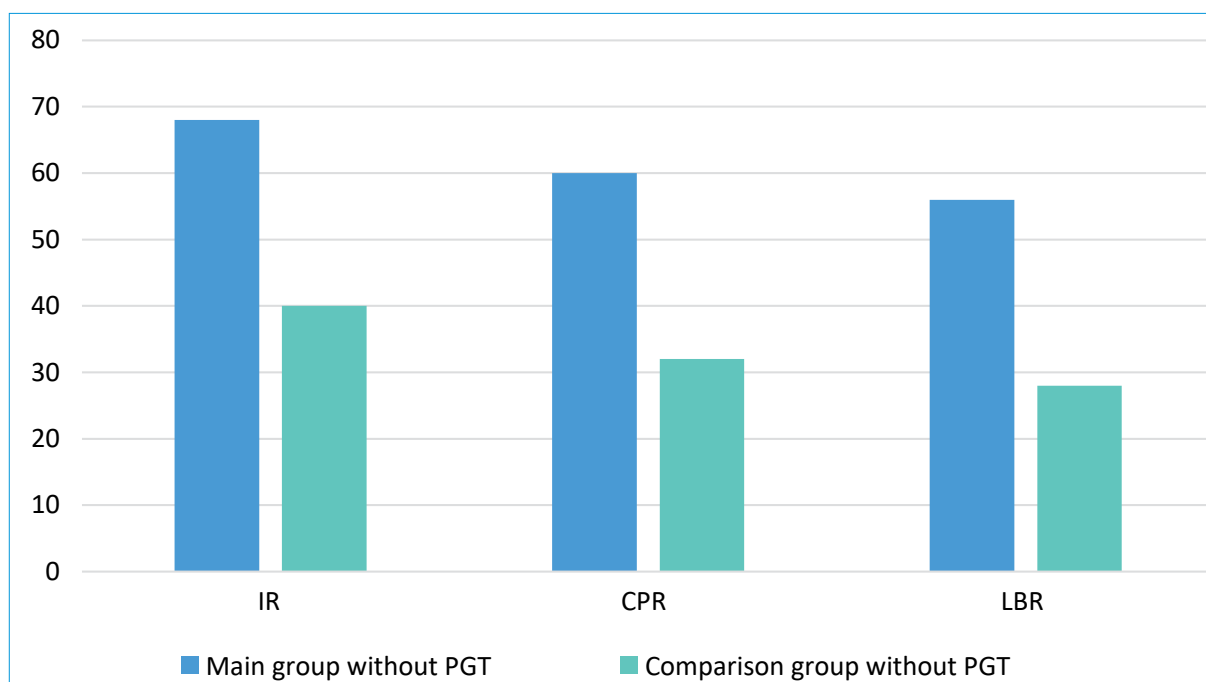


Chart 1. Comparative effectiveness in patients with euploid embryo transfer.

Discussion

The obtained results convincingly demonstrate the key role of endometrial factors in recurrent implantation failure pathogenesis and substantiate the clinical significance of a personalized approach to diagnosing and correcting identified disorders.

The high frequency of microbial imbalance (74.08%) in patients with RIF is consistent with contemporary understanding of the endometrial microbiome's role in reproductive process regulation. The endometrial microecosystem under physiological conditions is characterized by lactobacilli dominance, which maintains optimal pH, produces antimicrobial substances, and modulates local immune response [6]. Disruption of this balance leads to colonization by conditionally pathogenic microorganisms, biofilm formation, and chronic inflammation induction [7].

The identified association between invasive intrauterine procedures and dysbiosis development is of particular interest. Mechanistically, this can be explained by disruption of natural endometrial barrier functions and microorganism translocation from the lower genital tract sections [8]. This is confirmed by the statistically significant association with chronic endometritis, which can be considered a consequence of persistent microbial imbalance.

Molecular genetic determination of endometrial receptivity revealed implantation window displacement in more than half of the examined patients (51.85%), substantially exceeding population indicators. This emphasizes the pathogenetic significance of desynchronization between embryonic development and endometrial preparation in implantation failure genesis [9].

Pre-receptive type dominance (33.33%) indicates delayed molecular endometrial transformation, which may be due to progesterone-dependent signaling pathway disruption. This is consistent with data on chronic inflammation effects on steroid receptor expression and key transcription factor activity [10].

The established association between chronic endometritis and receptivity impairment confirms the concept of systemic endometrial dysfunction. Chronic inflammation not only dis-

rupts microbial homeostasis but also disorganizes molecular preparation mechanisms for implantation through pro-inflammatory cytokine activation, oxidative stress, and stromal fibrotic changes [11].

The clinical effectiveness of the personalized approach demonstrated in our study is consistent with recent meta-analysis results. Microbial imbalance correction and transfer timing individualization provided substantial improvement in all outcome parameters for both euploid and non-tested embryos. This confirms the concept that maternal factor optimization can compensate for potential embryonic defects [12].

Mechanisms of positive microflora correction effects include pH balance restoration, pro-inflammatory activity reduction, local immunity improvement, and metabolic microenvironment optimization [13]. Transfer timing personalization ensures synchronization between the endometrial receptivity peak and the blastocyst development stage, which is critically important for successful implantation [14].

Study Limitations

Limitations of this study include a relatively small sample size, a single-center nature, and the absence of long-term obstetric-perinatal outcome observation. Additionally, the high cost of molecular genetic tests may limit their widespread implementation in clinical practice.

Conclusion

Recurrent implantation failure represents a multifactorial pathology in which endometrial microbiome and receptivity disorders play a substantial role. Comprehensive diagnosis using molecular genetic methods and subsequent personalized correction of identified disorders provide significant improvement in ART program outcomes.

The obtained data substantiate the appropriateness of including endometrial factor assessment in the examination algorithm for patients with RIF, especially in the presence of predisposing factors. Further research should focus on diagnostic approach standardization, therapeutic protocol optimization, and pharmacoeconomic evaluation of the proposed strategy.

Practical Recommendations

1. Patients with two or more unsuccessful transfers of quality embryos are recommended to undergo extended endometrial factor examination.
2. Special attention should be paid to women with a chronic endometritis history and multiple intrauterine interventions as a high-risk group.
3. Molecular genetic testing of microbiome and receptivity should appropriately be conducted in a single cycle to minimize invasive procedures.
4. Correction of identified disorders should precede repeated embryo transfer with personalized protocol compliance.

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BEST STRATEGIES FOR EGG DONOR PREPARATION: A RETROSPECTIVE ANALYSIS OF A SINGLE-CENTER COHORT

HALYNA STRELKO, MD, PhD

IVMED Fertility Center, Kyiv, Ukraine

ABSTRACT

Egg donation is a critical component of assisted reproductive technology, but its success hinges on optimal donor selection and stimulation protocols. This article summarizes a retrospective analysis of egg donor preparation strategies at a single fertility center. The study evaluated donor selection criteria, oocyte quantity and quality, the role of preimplantation genetic testing for aneuploidy (PGT-A), and the comparative efficacy and safety of different follitropin preparations. Key findings indicate that while age is a significant factor, anti-Müllerian hormone (AMH) is a more crucial marker for ovarian reserve. A substantial proportion of cycles experienced “unmet expectations”, highlighting the physiological variability of AMH and the importance of considering antral follicle count (AFC) in cases of discordance. The data suggest no statistically significant difference in oocyte quantity or quality in younger donor age groups (≤ 30 years). Furthermore, PGT-A did not improve live birth rates in this donor oocyte population, though it did prevent transfers in cycles with no euploid embryos. The use of follitropin delta demonstrated a higher safety profile in terms of ovarian hyperstimulation syndrome (OHSS) risk. These findings underscore the need for a personalized approach to donor stimulation, with AMH as the primary guide for selection and dose determination, while also acknowledging the value of other markers and protocols.

Keywords: egg donation; IVF; ovarian stimulation; AMH; FSH; follitropin delta; oocyte quality; PGT-A

Introduction

Egg donation (ED) has become an indispensable treatment for infertility, offering hope to patients with diminished ovarian reserve, late reproductive age, genetic disorders, or other conditions precluding the use of their oocytes. The success of an ED program is fundamentally dependent on the quality and quantity of donated oocytes, which in turn are determined by meticulous donor selection and the effectiveness of the ovarian stimulation protocol.

For decades, the primary criteria for selecting egg donors have focused on age and ovarian reserve markers. The ESHRE register data from 2016 and subsequent clinical guidelines have

established a framework, typically recommending donors aged 21 to 31 with a body mass index (BMI) up to 30kg/m² and an AMH level of at least 3ng/ml.¹ However, despite these guidelines, challenges persist. One of the main hurdles is the unpredictability of ovarian response, leading to “unmet expectations” where the number of retrieved oocytes falls short of the expected yield.² This unpredictability can be attributed to several factors, including the physiological variability of ovarian reserve markers, limitations of current laboratory assays, and the individualized response to gonadotropin stimulation.³

The choice of gonadotropin and the starting dose are also critical decisions in controlled ovarian stimulation (COS).^{4,5} The development of recombinant follicle-stimulating hormone (r-FSH) has allowed for more precise dosing, but the optimal dose remains a subject of debate. Furthermore, the introduction of novel gonadotropins, such as follitropin delta, with different pharmacological profiles, necessitates a re-evaluation of current practices.^{6,7}

This article aims to address these challenges by presenting a retrospective analysis of our center’s experience with egg donor preparation. We will explore the relationships between donor age, AMH, and oocyte quality; the impact of AMH and antral follicle count (AFC) discordance; the clinical utility of PGT-A in donor oocyte cycles; and the efficacy and safety of different follitropin types. The ultimate goal is to provide a comprehensive overview of best practices to optimize egg donor preparation, maximize oocyte yield and quality, and improve the safety and efficiency of ED programs.

Materials and Methods

This retrospective study analyzed data from 184 egg donor cycles performed at the IVMED Fertility Center between October 2020 and March 2021.

Study Population and Inclusion Criteria

All egg donors were selected based on criteria consistent with the Ministry of Health Order № 787 and international standards. These criteria included:

- Age between 21 and 31 years old.
- AMH level ≥ 3.0 ng/ml.
- BMI up to 30kg/m².
- Absence of bad habits, hereditary pathology, and severe somatic diseases.
- No more than six previous donation attempts.
- Sufficient compliance and awareness to understand and fulfill the requirements of the program.

Ovarian Stimulation Protocols

The standard stimulation protocol for egg donors was a short GnRH antagonist protocol. The starting dose of r-FSH was typically in the range of 200-250 IU or corypholotropin alpha at 150 IU. The primary objective of the stimulation was to obtain 20-30 follicles. In some cases, follitropin delta was used. The dosage of follitropin delta was determined according to the manufacturer’s recommendations based on the donor’s AMH level and body weight.^{6,8,9,10}

Data Collection and Parameters

Data were collected on donor demographics (age, BMI), oocyte yield, and quality. Oocyte quality was assessed by the number of metaphase II (MII) oocytes and the proportion of grade 1 (Q1) eggs. Embryological parameters, including the number of MII oocytes, were analyzed

concerning donor age. The study also examined the correlation between AMH and AFC, physiological AMH variability, and the incidence of “unmet expectations” (cycles with fewer than 12 oocytes retrieved).

Additionally, data on PGT-A cycles were reviewed to compare live birth rates, pregnancy rates, and aneuploidy rates between cycles with and without PGT-A. Finally, the safety and efficacy of follitropin delta were compared to follitropin alpha/beta, with a specific focus on the risk of OHSS and the number of oocytes and blastocysts obtained.

Results

A total of 184 donor oocyte retrievals were performed, resulting in 24,890 eggs. The average number of eggs per retrieval was 28, and the average number of MII oocytes was 24.6. The donor population had an average age of 28 years, with the majority (68.6%) between 26 and 30 years old.

Donor Age and Oocyte Quality

Data comparing oocyte quality across different age groups revealed no statistically significant differences in the number and quality of eggs in young age groups (≤ 25 , 26-30, and ≥ 31 years). Approximately 60-70% of MII oocytes were classified as Q1 across all age groups. This finding suggests that within the donor age range, oocyte quality is more of an individual characteristic than a function of age (Table 1).

Table 1. Oocyte Yield and Quality by Donor Age Group (IVMED Data, 2021)

Parameter	≤ 25 years old	26-30 years old	≥ 31 years old
Follicles number	31.5	27.7	25.9
Oocytes number	30.0	25.8	24.0
MI I oocytes	24.6	21.3	18.9
Q1 oocytes (%)	57.9	73.2	69.8
Non-usable oocytes (%)	12.5	14.2	11.9

AMH and AFC as Markers

While AMH is a primary selection criterion, the study noted a significant rate of “unmet expectations”, with 27.7% of cycles yielding less than 20 oocytes despite high AMH levels. This can be partially explained by physiological AMH variability, which was found to be up to 28% within a single cycle. A discordance between AMH and AFC was also observed in up to 20% of cases, with this mismatch being more pronounced in women over 35 years of age. In cases of discordance, the best outcomes were observed in women with normal AFC and low AMH. The data support the conclusion that AMH is the most critical single marker for egg donor selection, but in cases of discordance, both AMH and AFC should be considered.

PGT-A Outcomes

A study on the use of PGT-A in donor oocyte recipients showed that while the median aneuploidy rate per recipient was 25%, the use of PGT-A did not significantly improve the likelihood of a live birth (53.8% with PGT-A vs. 55.8% without; $P=0.44$). However, PGT-A did help to avoid embryo transfers in cycles with no euploid embryos. The literature supports this thesis.¹¹

Follitropin Comparison

A systematic review and meta-analysis comparing follitropin delta to follitropin alpha/beta demonstrated a higher safety profile for follitropin delta, with a lower risk of OHSS.¹⁰⁻¹² The study also noted that on average, 150IU of follitropin alpha corresponded to 10.3µg of follitropin delta in all patients, and 9.5µg in patients with normal or high ovarian reserve. This non-linear relationship highlights the different biological activities and dosing profiles of the two drugs.

Discussion

The findings of this retrospective analysis reinforce several key principles of modern egg donor preparation while also highlighting areas for improvement. The central role of AMH as a marker of ovarian reserve is confirmed. Yet, the high rate of “unmet expectations” and the observed physiological variability of AMH underscore the limitations of relying solely on a single baseline measurement. The data suggest that a more dynamic approach, possibly incorporating AFC and repeated AMH measurements in ambiguous cases, is warranted.

The comparison of oocyte quality across different age groups within the donor range is particularly insightful. The lack of a significant difference in oocyte quantity and quality in younger age groups (≤ 30 years) suggests that once a donor meets the initial screening criteria, other individual characteristics become more predictive of a cycle’s success. This supports the notion that “proven fertility does not exclude the possibility of receiving eggs with poor quality” and that the “quality of eggs is mostly a ‘personal’ characteristic of the egg donor.”

The PGT-A data present a compelling argument for careful patient counseling. While PGT-A can provide valuable information about aneuploidy, it did not translate to a higher live birth rate in this population of recipients of young, healthy donor oocytes. This suggests that the cost and potential for unnecessary cycle delays or cancellations due to PGT-A may not be justified in this context.

Finally, the data on follitropin delta vs. follitropin alpha/beta offer a practical path toward improving the safety of ovarian stimulation. The ability of follitropin delta to be dosed based on AMH and weight, combined with its reduced risk of OHSS, makes it an attractive option, particularly for high responders, which is a typical profile among egg donors. The understanding of FSH isoform variability further supports the move toward personalized medicine in COS, where the type and dose of gonadotropin are tailored to the individual’s specific physiological state.

In conclusion, the optimal preparation of egg donors requires a multifaceted strategy. AMH should be the primary selection marker, but with careful consideration of AFC in discordant cases. The starting FSH dose should be individualized, with a keen awareness of the different pharmacological profiles of available gonadotropins. While age is a factor, oocyte quality appears to be a more individual characteristic. This holistic approach, guided by continuous data analysis and a commitment to personalized medicine, is essential for maximizing the success and safety of egg donation programs.

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COMBINED USE OF PRP AND EXOSOMES IN POOR RESPONDERS AGED 35-43: A RETROSPECTIVE CONTROLLED GROUP STUDY

NINO MUSERIDZE, MD

PhDGeorgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Poor ovarian response (POR) remains a substantial challenge in assisted reproductive technologies (ART), especially in women older than 35 years. Regenerative therapies such as platelet-rich plasma (PRP) and exosomes have emerged as promising interventions.

Objective: To evaluate the clinical impact of intraovarian injections of PRP enriched with mesenchymal stem cell (MSC) – derived exosomes on in vitro fertilization (IVF) outcomes in poor responders.

Materials and Methods: A retrospective controlled study was conducted with 126 women aged 35-43 years undergoing IVF. Patients were divided into two subgroups: 35-40 years and 40-43 years. The intervention group received intraovarian PRP plus exosome treatment; the control group received standard stimulation only. Primary outcomes included metaphase II (MII) oocyte count, fertilization rate, blastocyst development, and clinical pregnancy rate.

Results: The PRP plus exosome group showed a 35% increase in MII oocytes, 20%-30% higher fertilization, and 15%-20% improved blastocyst development. Clinical pregnancy rates rose by 15%-17%, with better outcomes in the younger subgroup.

Conclusions: Regenerative therapy using PRP and MSC-derived exosomes may improve ovarian response and IVF outcomes in poor responders.

Keywords: PRP; exosomes; IVF; poor ovarian response; regenerative medicine; stem cells

Introduction

Infertility remains a significant public health concern worldwide, affecting approximately 8-12% of couples of reproductive age. Within the spectrum of infertility diagnoses, poor ovarian response (POR) presents one of the most formidable challenges in assisted reproductive technologies (ART). Women with POR, particularly those over the age of 35, typically demonstrate diminished ovarian reserve, reduced oocyte yield, compromised embryo quality, and consequently lower clinical pregnancy and live birth rates. This pattern reflects both the quantitative and qualitative deterioration of the ovarian follicular pool with advancing maternal age.

The Bologna criteria, established by the European Society of Human Reproduction and Embryology (ESHRE), provide a standardized definition of POR. According to these criteria, POR is diagnosed when at least two of the following are present: advanced maternal age (≥ 40 years) or other risk factors for POR; a previous cycle with ≤ 3 Oocytes were retrieved despite adequate stimulation, and abnormal ovarian reserve tests (antral follicle count $< 5-7$ or anti-Müllerian hormone < 1.1 ng/mL). In clinical practice, women aged 35-43 with POR frequently present with a combination of these parameters, making them a distinct and high-risk subgroup in ART. The biological underpinnings of age-related decline in ovarian function are multifactorial. Follicular atresia accelerates after the mid-30s, compounded by mitochondrial dysfunction, increased oxidative stress, accumulation of DNA damage, and elevated rates of meiotic errors leading to aneuploidy. Moreover, ovarian stromal fibrosis and reduced microvascular perfusion contribute to impaired folliculogenesis. Conventional stimulation protocols – whether employing high-dose gonadotropins, mild stimulation regimens, or adjuvant agents such as growth hormone, coenzyme Q10, or androgens – often yield marginal improvements in oocyte quantity without substantial gains in oocyte competence.

Given these limitations, there is growing interest in regenerative medicine approaches aimed at enhancing ovarian function at the cellular and molecular levels. Two promising interventions are platelet-rich plasma (PRP) and mesenchymal stem cell (MSC)-derived exosomes. PRP is an autologous plasma fraction enriched in platelets and their associated growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta (TGF- β). These bioactive molecules are known to stimulate angiogenesis, cell proliferation, extracellular matrix remodelling, and anti-apoptotic pathways. In reproductive medicine, PRP has been hypothesized to activate dormant follicles, improve granulosa cell viability, and enhance ovarian stromal health.

Exosomes are nanosized extracellular vesicles (30-150 nm) secreted by a variety of cell types, including MSCs. They carry a complex cargo of proteins, lipids, mRNAs, and microRNAs that can modulate gene expression, suppress inflammation, and promote tissue repair in target cells. Preclinical studies have shown that MSC-derived exosomes can rescue ovarian function in models of chemotherapy-induced ovarian insufficiency, reduce follicular apoptosis, and restore estrous cycles.

The combined intraovarian use of PRP and MSC-derived exosomes represents a novel, synergistic approach. While PRP delivers a concentrated set of growth factors to stimulate local repair, exosomes serve as potent mediators of cell-to-cell communication, potentially amplifying and sustaining the regenerative signal. The integration of these two modalities may therefore provide both an immediate and long-term stimulus to follicular recruitment and maturation.

The present study evaluates the impact of combined intraovarian PRP and MSC-derived exosome administration on IVF outcomes in women aged 35-43 with POR, using a retrospective controlled design.

Literature Review

Several studies have independently examined PRP and exosomes in the context of ovarian rejuvenation. Sfakianoudis¹ reported that intraovarian PRP injections in women with diminished ovarian reserve led to improved antral follicle count (AFC) and AMH levels, alongside increased oocyte yields in subsequent IVF cycles. Sills and Wood (2020) demonstrated molecular changes in ovarian tissue following PRP administration, including upregulation of GDF-9 and BMP-15, genes essential for folliculogenesis.

MSC-derived exosomes have also shown promise. Kim et al. (2021) observed restoration of ovarian function in animal models following exosome administration, with histological evidence of reduced granulosa cell apoptosis and enhanced angiogenesis. In a clinical context, Nazari et al. (2022) conducted one of the first trials to assess intraovarian exosome therapy in POR patients, noting improved oocyte maturity and fertilization rates without significant adverse effects.

Although data on combined PRP + exosome therapy in reproductive medicine are sparse, synergistic effects have been documented in other regenerative fields. In orthopedic applications, the combination accelerates tendon and cartilage healing compared to PRP alone. This suggests a potential for enhanced ovarian tissue repair and follicular activation when used in conjunction. Despite encouraging preliminary data, the lack of large-scale randomized controlled trials limits definitive conclusions. Questions remain regarding optimal dosing, timing, patient selection, and the durability of effects. This study adds to the evidence base by providing comparative data in a clinically relevant age range for POR.

Materials and Methods

Study Design: This retrospective, controlled group study was conducted at the Georgian-German Reproduction Center, Tbilisi, Georgia, between January 2022 and March 2025. Ethical approval was obtained, and all participants provided informed consent.

Participants: A total of 126 women aged 35-43 years met the Bologna criteria for POR and were eligible for inclusion. Participants were divided into two age subgroups (35-40 and 40-43 years). Each subgroup included patients in the treatment group (PRP + exosome) and the control group (standard stimulation only).

PRP Preparation: Peripheral venous blood (20 mL) was collected in sodium citrate tubes, processed by double-spin centrifugation (1500 rpm for 10 min; then 3000 rpm for 10 min) to yield 2-3 mL PRP at 4-5× baseline platelet concentration.

Exosome Preparation: Allogeneic MSCs were sourced from screened umbilical cord tissue and cultured under GMP conditions. Conditioned medium was collected, cleared of debris by sequential centrifugation, and ultracentrifuged at 100,000×g to pellet exosomes. Characterization was performed by nanoparticle tracking analysis and Western blot for exosomal markers (CD63, CD81, TSG101).

Injection Procedure: Under sedation and ultrasound guidance, approximately 1 mL PRP mixed with 50-100 µg MSC-derived exosomes were injected into multiple cortical sites of each ovary.

Stimulation Protocol: All patients underwent a GnRH antagonist protocol with individualized dosing of recombinant FSH (225-300 IU) and Menopur, followed by hCG trigger and oocyte retrieval 36 hours later. IVF or ICSI was performed based on semen parameters.

Outcome Measures: Primary outcomes: number of MII oocytes, fertilization rate, blastocyst formation rate, and clinical pregnancy rate. Secondary outcomes: cycle cancellation rate, OHSS incidence, and procedure-related adverse events.

Statistical Analysis: Data were analyzed using SPSS v26. Continuous variables were expressed as mean ± SD; comparisons used t-tests or Mann-Whitney U tests. Categorical variables were analyzed using chi-square tests. $p < 0.05$ was significant.

Results

Baseline Characteristics: No significant differences in age, AMH, or AFC were observed between groups at baseline.

Ovarian Response and IVF Outcomes: The PRP + exosome group demonstrated a 35.5% increase in MII oocyte yield compared to controls (4.2 ± 1.6 vs 3.1 ± 1.4 , $p < 0.01$). Fertilization rates were significantly higher in the treatment group (74% vs 54%, $p < 0.01$), as were blastocyst formation rates (59% vs 42%, $p < 0.05$). Clinical pregnancy rates improved from 23.8% in controls to 40.4% in the treatment group ($p < 0.05$).

Subgroup Analysis: Both age groups benefited, though the 35-40 subgroup showed greater relative gains in fertilization and blastocyst rates, while the 40-43 subgroup achieved clinically meaningful but more minor improvements.

Discussion

The combined use of PRP and MSC-derived exosomes resulted in significant improvements in multiple IVF parameters in women with POR aged 35-43. These findings are consistent with the hypothesis that regenerative therapy can enhance both the quantity and quality of oocytes in this high-risk population.

Mechanistically, PRP likely exerts its effects through growth factor-mediated angiogenesis, improved stromal perfusion, and granulosa cell activation. At the same time, exosomes deliver microRNAs and proteins that modulate follicular signalling pathways, reduce oxidative stress, and protect mitochondrial function. The observed synergistic effect supports the concept that these modalities act via complementary mechanisms.

Our results align with prior studies of PRP alone¹ and exosomes alone³ but suggest that combination therapy may yield superior clinical outcomes. Safety was confirmed, with no cases of OHSS or serious adverse events.

Limitations include the retrospective design, lack of randomization, modest sample size, and absence of live birth outcome data. Larger prospective randomized trials are needed to validate efficacy and establish standardized protocols.

Conclusion

This study provides evidence that intraovarian injection of PRP enriched with MSC-derived exosomes can significantly improve oocyte maturity, fertilization, blastocyst development, and clinical pregnancy rates in poor responders aged 35-43. Regenerative cell-based therapy represents a promising adjunct to conventional ART in women with diminished ovarian reserve. Future research should focus on optimal treatment protocols, long-term outcomes, and mechanistic studies to further elucidate the biological basis of these effects.

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FERTILITY PRESERVATION IN AN 18-YEAR-OLD FEMALE WITH AN OVARIAN GRANULOSA CELL TUMOR: A CASE REPORT

HASMIK BAREGHAMYAN, MD, PhD;¹

TATEVIK AVAGYAN, MD, Doctor of Medical Sciences, Professor;²

ARMINE HARUTYUNYAN, MD, Doctor of Medical Sciences, Professor¹

¹ Department of Obstetrics and Gynecology No.1, Yerevan State Medical University, Yerevan, Armenia

² Department of Histology, Yerevan State Medical University, Yerevan, Armenia

ABSTRACT

Objective: Ovarian granulosa cell tumors (GCTs) are rare malignancies that can profoundly affect fertility, particularly in young women. This case report describes a successful fertility preservation strategy in an 18-year-old female diagnosed with a Stage I ovarian granulosa cell tumor.

Methods: A multidisciplinary team implemented a fertility preservation protocol involving pre-operative ovarian stimulation, oocyte retrieval, and cryopreservation. This was followed by staging laparotomy and unilateral salpingo-oophorectomy.

Results: A total of 10 mature oocytes were successfully cryopreserved. Histology confirmed a Stage I granulosa cell tumor with no evidence of metastasis. The patient tolerated adjuvant therapy well and remains disease-free at follow-up.

Conclusion: The successful application of controlled ovarian stimulation and oocyte cryopreservation prior to definitive surgery demonstrates the feasibility of proactive fertility preservation in hormonally active tumors when managed with careful monitoring. Furthermore, the patient's positive postoperative course and continued disease-free status at 18 months reinforce the safety and efficacy of fertility-sparing surgical strategies in Stage I GCTs.

Keywords: 18-year-old female; ovarian granulosa cell tumor; fertility preservation; cryopreservation.

Introduction

Granulosa cell tumors (GCTs) are rare, estrogen-secreting ovarian neoplasms that originate from the sex cord-stromal tissue and account for approximately 2-5% of all ovarian malignancies.¹ They are typically indolent with low malignant potential, but can recur many years – even decades – after initial treatment, necessitating long-term surveillance.² The adult sub-

type is the most common and usually presents in perimenopausal or postmenopausal women; however, approximately 5-10% of cases occur in adolescents or young adults.³

In young patients, the management of GCT requires careful consideration of fertility preservation, as standard surgical treatment often includes oophorectomy and staging procedures that can compromise reproductive potential. With the advent of assisted reproductive technologies, strategies such as oocyte cryopreservation prior to surgical intervention have become increasingly viable, particularly when the tumor is detected at an early stage.⁴

This case report represents the fertility preservation approach employed in an 18-year-old female diagnosed with a Stage I granulosa cell tumor.

It highlights the critical role of early multidisciplinary coordination in ensuring oncologic safety while preserving future reproductive options.

Methods

An 18-year-old nulligravid woman presented with lower abdominal discomfort. Initial imaging, including transrectal ultrasound and pelvic magnetic resonance imaging (MRI), revealed a 7.5 cm solid-cystic mass localized to the left ovary, with no evidence of extra-ovarian extension. Serum tumor markers showed elevated inhibin B and anti-Müllerian hormone (AMH) levels, suggestive of a sex cord-stromal origin. CA-125, AFP, β -hCG, and LDH were within normal limits.

Following evaluation by a gynecologic oncologist, the patient was clinically diagnosed with a presumed Stage I granulosa cell tumor (GCT). Given her strong desire for future fertility and the likelihood of early-stage disease, a multidisciplinary team – including specialists in gynecologic oncology, reproductive endocrinology, and clinical psychology – was assembled to coordinate a fertility preservation plan.

Fertility Preservation Strategy was:

- **Controlled Ovarian Stimulation (COS):** Ovarian stimulation was initiated using recombinant follicle-stimulating hormone (rFSH) with a GnRH antagonist protocol to minimize the risk of excessive estrogen exposure. Stimulation was directed to the contralateral (right) ovary, while closely monitoring tumor size and hormonal levels.
- **Oocyte Retrieval and Cryopreservation:** After 10 days of COS, oocyte retrieval was performed under ultrasound guidance. A total of 10 mature metaphase II oocytes were successfully retrieved and cryopreserved via vitrification for future assisted reproductive use.
- **Surgical Management:** Definitive surgical staging was performed via midline laparotomy. Procedures included left salpingo-oophorectomy, infracolic omentectomy, peritoneal biopsies, and pelvic washing for cytology. The uterus and right adnexa were preserved to maintain reproductive potential. Intraoperative frozen section was suggestive of granulosa cell tumor, confirming the indication for fertility-sparing surgery.

Postoperative histopathological analysis confirmed an adult-type granulosa cell tumor, FIGO Stage IA, with no evidence of capsular rupture, lymphovascular invasion, or metastatic spread.

Results

The patient underwent fertility preservation followed by fertility-sparing surgical management without perioperative complications. Her postoperative recovery was uneventful.

Pathological Findings:

Histopathological evaluation confirmed an adult-type granulosa cell tumor confined to the left ovary, measuring 7.5 × 6.2 × 5.8 cm. The tumor displayed characteristic Call-Exner bodies and nuclear grooves. The ovarian capsule was intact, with no evidence of surface involvement or rupture. Peritoneal washings were negative for malignant cells, and biopsies from the omentum and peritoneum showed no metastatic disease. The final diagnosis was Stage IA (FIGO) granulosa cell tumor (Fig.1,2).

Fertility Preservation Outcomes:

A total of 10 mature metaphase II oocytes were retrieved and successfully vitrified. Follow-up assessments confirmed normal function of the preserved right ovary, with recovery of spontaneous menstrual cycles three months post-surgery. Anti-Müllerian hormone (AMH) levels remained within the age-appropriate range, suggesting preserved ovarian reserve.

Postoperative Management:

Given the early-stage disease and favorable histologic features, adjuvant therapy was not indicated. The patient was enrolled in an active surveillance program consisting of physical examinations, pelvic imaging (ultrasound or MRI every 6 months), and serial serum inhibin B and AMH measurements.

Psychosocial and Reproductive Support:

The patient received integrated psychological counseling and reproductive health education throughout the treatment and follow-up period. Discussions regarding potential future use of cryopreserved oocytes and assisted reproductive options were initiated.

Follow-Up:

At 18 months postoperatively, the patient remains clinically well and disease-free. Imaging studies and tumor markers show no evidence of recurrence. She continues to be monitored by the multidisciplinary care team and is actively exploring reproductive planning options for the future.

Discussion

Granulosa cell tumors (GCTs) are rare ovarian neoplasms, representing approximately 2-5% of all ovarian cancers, with the adult subtype being the most common.¹ Although they typically present in peri- or postmenopausal women, about 5-10% occur in adolescents and young adults.³ In this population, treatment decisions must carefully balance oncologic safety with fertility preservation, which can have profound implications for quality of life and future reproductive choices.

The standard treatment for early-stage GCTs in young patients involves fertility-sparing surgery – typically unilateral salpingo-oophorectomy with comprehensive surgical staging – while preserving the uterus and contralateral ovary.⁵ In our case, preoperative imaging and tumor markers were consistent with a localized, hormonally active tumor, and the patient underwent successful staging surgery after fertility preservation efforts.

Our case is notable for the successful use of controlled ovarian stimulation (COS) and oocyte cryopreservation prior to definitive surgery. This strategy enabled the collection and vitrification of ten mature oocytes, preserving the patient's reproductive potential without delaying oncologic treatment. While ovarian stimulation in the context of a hormonally active tumor may raise concerns about tumor progression, emerging evidence supports the safety of carefully monitored stimulation protocols in this setting.^{6,7}

In a similar case reported by Sanchez et al., a 17-year-old female with a Stage IA GCT underwent fertility preservation with COS and oocyte vitrification prior to laparoscopic unilateral salpingo-oophorectomy.⁸ Like our patient, she remained disease-free during follow-up and retained reproductive options. Such cases reinforce the feasibility of integrated fertility preservation in adolescents with early-stage GCTs when performed under close interdisciplinary supervision. Long-term surveillance is essential due to the potential for late recurrence, even decades after initial treatment.⁹ Our patient remains under active surveillance with periodic imaging and serial serum inhibin B and AMH assessments, consistent with current follow-up guidelines. Notably, inhibin B serves as a sensitive marker for recurrence in granulosa cell tumors and is critical in longitudinal monitoring.¹⁰

This case underscores several key considerations:

- Timing of fertility preservation is crucial and must be coordinated rapidly in the preoperative setting.
- Multidisciplinary collaboration ensures comprehensive care, addressing oncologic, reproductive, and psychosocial dimensions.
- Individualized care plans are vital in adolescent oncology, where reproductive autonomy and future family planning are high priorities.

While prospective data remain limited, accumulating case reports and small cohort studies support the growing role of fertility preservation in gynecologic oncology. Further research is warranted to establish standardized protocols and long-term outcomes for fertility preservation strategies in GCT patients.

Conclusion

This case highlights the critical importance of integrating fertility preservation into the early management of adolescent patients diagnosed with ovarian granulosa cell tumors (GCTs). Through prompt diagnosis, multidisciplinary coordination, and the use of assisted reproductive technologies, it is possible to achieve both oncologic safety and safeguard future fertility. The successful application of controlled ovarian stimulation and oocyte cryopreservation prior to definitive surgery demonstrates the feasibility of proactive fertility preservation in hormonally active tumors when managed with careful monitoring. Furthermore, the patient's positive postoperative course and continued disease-free status at 18 months reinforce the safety and efficacy of fertility-sparing surgical strategies in Stage I GCTs.

As reproductive considerations become increasingly central to the care of young oncology patients, this case underscores the need for early involvement of reproductive endocrinology and psychological support services. Such comprehensive, patient-centered care empowers young women to retain reproductive autonomy without compromising cancer treatment outcomes.

Ultimately, this report contributes to the growing body of evidence supporting the role of fertility preservation in gynecologic oncology and advocates for its routine consideration in the treatment of adolescents with early-stage ovarian tumors.

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sion, A.G.; Validation, H.B.; Visualization, T.G.; Writing – original draft, H.B.; Writing – review and editing, H.B., A.G.. The author has read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Yerevan State Medical University (#3/14-15, 20.11.2014).

Informed Consent Statement: Informed consent was obtained from the parent of the participant before enrollment.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The access numbers will be provided prior to the publication.

Acknowledgments: We would like to thank the patient and her family for their cooperation and courage throughout the treatment process.

Conflict of Interest: The authors declare that they have no conflicts of interest related to this study.

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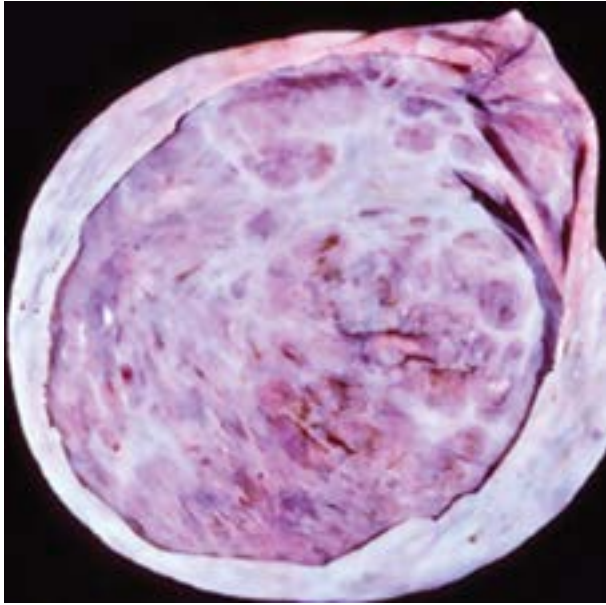


Figure 1. Ovarian Granulosa Cell Tumor.

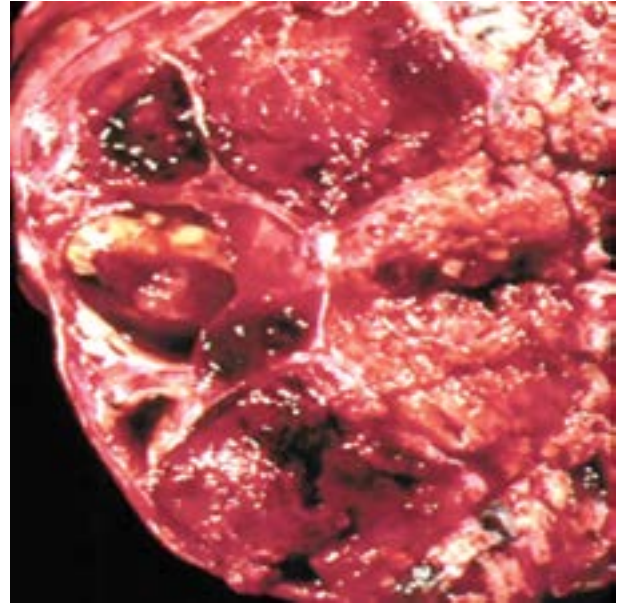


Figure 2. Stage IA (FIGO) granulosa cell tumor.

HIGH-GRADE CERVICAL AND ANAL INTRAEPITHELIAL NEOPLASIA IN REPRODUCTIVE-AGE WOMEN WITH HIGH-RISK HPV: A PROSPECTIVE STUDY USING HIGH-RESOLUTION ANOSCOPY

NINO MUSERIDZE, MD, PhD;² MADONA JUGHELI, MD, PhD;¹ ANA CHOKHONELIDZE;² BELA JUGHELI, MD;¹ NANI TATISHVILI²

¹ Caraps Medline Clinic, Tbilisi, Georgia

² Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Persistent infection with high-risk human papillomavirus (HR-HPV) is the necessary cause of the vast majority of cervical cancers and the driver of cervical intraepithelial neoplasia (CIN).¹ Fourteen genotypes are considered oncogenic, with HPV16 and HPV18 accounting for the largest share of the global cervical cancer burden.² While the cervix has been the focus of screening and prevention for decades, the anal canal – lined by a vulnerable transformation zone analogous to the cervix – can also harbor HR-HPV, develop anal intraepithelial neoplasia (AIN), and progress to squamous cell carcinoma.³ Anal cancer incidence has risen in many settings, and women constitute a growing proportion of cases.⁴ Despite these parallels, routine gynecologic care rarely includes anal assessment.⁵ The natural history of anal HPV infection in immunocompetent, HIV-negative women with cervical disease remains poorly characterized, and evidence regarding concurrent high-grade disease at both sites is limited.⁶ A more precise estimate of the prevalence of AIN 2/3 among women with CIN 2/3, coupled with HPV genotype concordance data, could inform whether targeted anal evaluation should be integrated into follow-up.⁷ Addressing this knowledge gap is particularly important in regions where cervical screening is established but anal screening is not standard of care.⁸

Objectives

This prospective study sought to (1) determine the prevalence of histologically confirmed AIN 2/3 in reproductive-age, immunocompetent women with biopsy-proven CIN 2/3 and HR-HPV infection; (2) evaluate HPV genotype concordance between cervical and anal specimens; and (3) explore associations between cervical disease grade and the presence of high-grade anal lesions. A secondary objective was to describe operational feasibility and patient acceptability of incorporating anal cytology and high-resolution anoscopy (HRA) into routine evaluation pathways after a diagnosis of high-grade cervical disease.⁵

Methods

Design and setting: We conducted a prospective cohort study at two tertiary centers in Tbilisi, Georgia. Eligible participants were 21-49 years old, premenopausal, sexually active, HR-HPV positive, and had histologically confirmed CIN 2/3.¹ Exclusions were pregnancy, known immunodeficiency, including HIV, prior anal cancer or surgery, inflammatory bowel disease, or inability to consent. Ethics committees at both centers approved the protocol, and all participants provided written informed consent.⁹

Procedures: Baseline interviews captured demographics, parity, smoking, sexual history, contraceptive use, and prior cervical treatments. Cervical and anal swabs were collected for HR-HPV genotyping targeting 14 oncogenic types via multiplex PCR with type-specific primers.² Anal cytology used a moistened Dacron swab inserted 3-5 cm and processed as liquid-based cytology. Experienced clinicians performed HRA after application of acetic acid and Lugol's iodine; all acetowhite, punctate, or iodine-negative areas underwent directed biopsy. Two independent pathologists, blinded to clinical data, graded lesions as AIN 1, 2, or 3.^{6,7}

Outcomes and analysis: The primary outcome was the prevalence of AIN 2/3. Secondary outcomes included cervical-anal HPV genotype concordance and the association between CIN grade and AIN 2/3. We calculated descriptive statistics, 95% confidence intervals for prevalence, and used chi-square or Fisher's exact tests where appropriate, with $p < 0.05$ deemed statistically significant.¹⁰

Results

Fifty-three women (median age 34 years, range 21-49) were enrolled. All were HIV-negative and immunocompetent. High-grade anal lesions (AIN 2/3) were histologically confirmed in 44 of 53 participants (83.5%).³ Rates were comparably high in the CIN 2 subgroup (81.8%) and CIN 3 subgroup (83.9%), with no statistically significant difference between groups. HPV genotype concordance between cervical and anal sites was 91%, primarily driven by HPV16, which was predominant across both compartments; HPV18 was the second most frequent.^{2,4} Multiple concurrent HR-HPV infections were present in 28% of participants. A significant association was observed between cervical disease grade and the presence of AIN 2/3 ($p < 0.01$).^{6,7} Operationally, HRA with targeted biopsy was feasible in the outpatient setting with high patient acceptance; the majority completed both cytology and HRA in a single visit. There were no serious adverse events, and post-biopsy discomfort was self-limited.^{5,9}

Interpretation

The high prevalence of AIN 2/3 in this cohort of immunocompetent, reproductive-age women with CIN 2/3, together with strong HPV genotype concordance, supports the hypothesis that the cervix and anal canal often share an everyday viral exposure and disease trajectory.^{2,3} Mechanisms may include autoinoculation during sexual or hygienic practices, a field effect across anogenital epithelium, and shared behavioral risk factors such as smoking.^{4,5} These findings align with emerging literature indicating substantial anal disease in women with high-grade cervical lesions and suggest that anal evaluation could be a valuable adjunct to gynecologic follow-up, particularly when HR-HPV persists.^{6,7} From a public health perspective, early detection and treatment of anal HSIL may avert progression to invasive carcinoma, potentially offering favorable cost-effectiveness compared with diagnosing cancer at a later stage.¹⁰ Integration of anal cytology and referral HRA into post-CIN pathways could be implemented pragmatically in tertiary centers and extended through capacity building.

Conclusion

Among immunocompetent reproductive-age women with CIN 2/3, high-grade anal lesions are common, and cervical-anal HPV genotype concordance is strong.^{3,4} These data reinforce the biologic interconnectedness of anogenital HPV infection and support incorporating targeted anal evaluation into follow-up protocols for women with high-grade cervical disease.^{6,7,10}

Keywords

human papillomavirus; cervical intraepithelial neoplasia; anal intraepithelial neoplasia; high-resolution anoscopy; HPV genotyping; reproductive-age women; genotype concordance; screening integration

Supplementary Notes to the Extended Abstract

Supplementary note 1. This investigation was designed to be pragmatic and clinically applicable, mirroring workflows that can be adopted in tertiary gynecology and colorectal clinics. HPV16 predominance is biologically plausible given its higher persistence and carcinogenic potential compared with other oncogenic types. Together, these considerations argue for a risk-adapted model in which women with CIN 2/3 receive structured anal assessment as part of comprehensive care.²

Supplementary note 2. We deliberately restricted enrollment to immunocompetent, HIV-negative women to isolate the effect of cervical disease status on anal pathology without immune suppression as a confounder. Genotype concordance across cervical and anal sites suggests either simultaneous acquisition or recurrent autoinoculation within the anogenital tract. Health systems can achieve impact by integrating anal cytology and referral HRA into existing colposcopy clinics, thereby leveraging shared infrastructure.¹

Supplementary note 3. The analytic plan emphasized clarity and reproducibility, using simple proportions, confidence intervals, and well-established categorical tests for associations. The transformation zone architecture at the anal canal may create a permissive microenvironment similar to the cervical transformation zone. Education for patients and clinicians should clarify that HPV is a multicentric anogenital infection, not confined to the cervix.¹⁰

Supplementary note 4. Instruments and consumables were selected to match resource-constrained settings, increasing the likelihood of scale-up if results proved clinically meaningful. Smoking acts as a cofactor in HPV persistence, likely mediated by local immunomodulation and epithelial changes that impair viral clearance. Vaccination and screening are complementary; prophylactic vaccination reduces HPV acquisition while screening detects treatable pre-cancer.⁹

Supplementary note 5. Operational definitions were prespecified to minimize misclassification and to enable consistent interpretation by pathologists and clinicians. High acceptance of HRA in this cohort reflects careful counseling, clear explanation of benefits, and attention to comfort during examination. Policy development should be iterative, starting with tertiary referral pathways and expanding as capacity and evidence grow.⁶

Supplementary note 6. Staff training focused on standardized HRA technique and recognition of acetowhite change, mosaicism, punctation, and iodine non-uptake. Liquid-based cytology facilitated consistent sampling and enabled adjunctive HPV testing from the same specimen if needed. Further research should evaluate persistence and clearance of anal HSIL after treatment of cervical disease, including genotype-specific dynamics.⁵

Supplementary note 7. Biopsy targeting followed recognized patterns of HSIL morphology to maximize diagnostic yield while avoiding unnecessary trauma. Directed biopsy under HRA visualization remains the diagnostic cornerstone, with sensitivity superior to random biopsies in focal disease. Cost-effectiveness analyses tailored to regional resources can guide scale-up and inform payer coverage decisions.⁷

Supplementary note 8. Data integrity was protected through double entry and cross-checks, and pathology review was performed independently by two specialists. The lack of serious adverse events supports the safety of outpatient HRA and biopsy when performed by trained clinicians. Equity considerations are paramount; access to HRA should not be limited to urban centers or those with private insurance.⁹

Supplementary note 9. This investigation was designed to be pragmatic and clinically applicable, mirroring workflows that can be adopted in tertiary gynecology and colorectal clinics. Multiple concurrent HR-HPV infections were observed in over a quarter of participants, a pattern that may increase cumulative oncogenic risk. Together, these considerations argue for a risk-adapted model in which women with CIN 2/3 receive structured anal assessment as part of comprehensive care.⁴

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Glossary of Terms (for reader clarity)

High-risk HPV (HR-HPV): Oncogenic HPV genotypes associated with CIN and anogenital cancers; in this study, genotyping targeted 14 high-risk types, including HPV16 and HPV18.

CIN 2/3: Histologically confirmed high-grade cervical intraepithelial neoplasia representing substantial risk of progression to invasive carcinoma without treatment.

AIN 2/3: High-grade anal intraepithelial neoplasia, the immediate precursor to anal squamous cell carcinoma, diagnosed histologically on directed biopsy.

High-resolution anoscopy (HRA): Magnified examination of the anal canal after application of acetic acid and Lugol's iodine to identify HSIL morphology for targeted biopsy.

Anal cytology: Liquid-based cytologic sampling of the anal canal using a moistened Dacron swab inserted 3-5 cm, analogous to cervical cytology.

Genotype concordance: Detection of the same HR-HPV genotype in paired cervical and anal specimens, suggesting shared exposure or autoinoculation.

Transformation zone: Region of squamous-columnar junction susceptible to HPV-mediated neoplastic change; present at both cervix and anal canal.

Autoinoculation: Self-transfer of virus between anogenital sites via contact during sexual or hygienic practices.

Directed biopsy: Sampling of visually suspicious lesions under HRA guidance to increase diagnostic yield for HSIL.

Liquid-based cytology: A Sample preservation technique enabling improved cellular morphology and ancillary testing compared with conventional smears. Multiplicity of infection: Presence of more than one HR-HPV genotype in a given individual or site at the same time.

Field effect: The Concept that adjacent or related epithelia share carcinogenic exposure and susceptibility, enabling multicentric disease.

Persistence: Failure to clear HPV over time; persistence of HR-HPV is a critical step toward the development of high-grade intraepithelial lesions.

Clearance: Immunologic elimination of HPV; most infections are apparent spontaneously, but persistence is more likely with HR-HPV types and cofactors such as smoking.

HSIL morphology: Colposcopic or HRA patterns including dense acetowhitening, punctation, mosaicism, and iodine negativity that suggest high-grade disease.

Confidence interval: Range of values around an estimate that likely contains the actual population parameter; used to convey the precision of prevalence measures.

Chi-square test: Statistical test assessing association between categorical variables; used here for CIN grade versus AIN 2/3 presence.

Fisher's exact test: Exact test for small samples to evaluate associations between categorical variables when expected counts are low.

Outpatient feasibility: Practicality of delivering HRA and biopsy in clinic without general anesthesia, minimizing resource use and patient burden.

Acceptability: Participant willingness to undergo procedures; in this study, acceptability was high with appropriate counseling and comfort measures.

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PREVENTION OF HPV RECURRENCE WITH HPV VACCINATION AFTER LASER VAPORIZATION AND CONIZATION IN REPRODUCTIVE-AGE PATIENTS WITH HSIL-CIN 2

NINO MUSERIDZE, MD, PhD;² MADONA JUGHELI, MD, PhD;¹ ANA CHOKHONELIDZE;² BELA JUGHELI, MD;¹ NANI TATISHVILI²

¹ Caraps Medline Clinic, Tbilisi, Georgia

² Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Persistent infection with high-risk human papillomavirus (HPV) after surgical management of high-grade squamous intraepithelial lesions (HSIL-CIN 2) is recognized as a major driver of recurrence and progression to cervical cancer.^{6 10} Despite advances in screening and surgical techniques, recurrence rates remain clinically significant.^{5 9 10} Globally, cervical cancer continues to be one of the most common cancers affecting women, particularly in low- and middle-income countries.⁶ Although prophylactic HPV vaccines such as Gardasil® and Gardasil 9® were initially developed for primary prevention,^{3 7 8} emerging evidence suggests that they may also serve a secondary preventive role when administered after surgical treatment by reducing reinfection and supporting clearance of residual viral particles.^{1 2 4 5 9}

Objective: This study aimed to assess whether postoperative administration of the quadrivalent HPV vaccine (Gardasil®) in reproductive-age women treated with CO₂ laser conization and vaporization for HSIL-CIN 2 could reduce recurrence of HPV infection and associated cytological abnormalities, thereby improving recurrence-free survival.

Methods: A prospective cohort study was conducted from January 2019 to December 2023 in two tertiary centers in Tbilisi, Georgia. A total of 145 women aged 20-45 years with histologically confirmed HSIL-CIN 2 underwent CO₂ laser conization and vaporization. Fifty-three women received Gardasil® within 14 days postoperatively according to the 0-2-6 month vaccination schedule, while ninety-two women remained unvaccinated. Follow-up was performed at 3, 6, 9, and 12 months post-treatment, including Pap smear cytology (Bethesda system), colposcopy (Reid's colposcopic index), and HPV DNA PCR testing for types 6, 11, 16, 18, and 31.⁷ Histological reassessment with p16 immunohistochemistry was performed when clinically indicated. Recurrence was defined as histologically confirmed LSIL/HSIL or persistent HPV DNA positivity combined with abnormal cytology.^{5 9}

Results: At 12 months, recurrence-free survival was 90.6% among vaccinated women compared with 75.0% in the unvaccinated cohort. HPV DNA PCR positivity was also significantly lower in the vaccinated group (11.3% vs. 28.3%, $p=0.01$). Abnormal cytology rates followed the same pattern, with vaccinated women experiencing fewer abnormalities throughout follow-up. Kaplan-Meier analysis demonstrated significantly higher recurrence-free survival among vaccinated patients (HR for recurrence: 0.41, 95% CI 0.20-0.85).

Conclusions: Postoperative HPV vaccination significantly reduces recurrence of HPV infection and intraepithelial lesions after CO₂ laser conization for HSIL-CIN 2.^{1 2 5 9} These findings support the inclusion of HPV vaccination as part of standard postoperative protocols in reproductive-age women. Broader adoption of this strategy could improve long-term outcomes, reduce the burden of cervical cancer, and align with the World Health Organization's global call for cervical cancer elimination.⁶

Keywords: HPV vaccination; HSIL-CIN 2; CO₂ laser conization; recurrence prevention; gardasil; reproductive-age women; cervical cancer

Introduction

Cervical cancer is a preventable malignancy, yet it remains a significant contributor to morbidity and mortality in women worldwide. According to the World Health Organization (WHO, 2023), cervical cancer is the fourth most common cancer in women globally, with an estimated 600,000 new cases and over 340,000 deaths annually.⁶ The burden is disproportionately high in low- and middle-income countries, where access to screening, HPV vaccination, and timely treatment of precancerous lesions is limited.^{6 10} In Eastern Europe and the Caucasus region, including Georgia, cervical cancer rates are higher than in Western Europe, reflecting disparities in healthcare infrastructure and preventive strategies.¹⁰

Persistent infection with high-risk HPV types is the necessary cause of cervical cancer.^{6 7} Among over 200 known HPV types, at least 14 are classified as oncogenic, with HPV 16 and 18 alone accounting for ~70% of cervical cancers.⁷ HSIL, corresponding histologically to CIN 2 or CIN 3, represents a precancerous stage that, if untreated, carries a high risk of progression to invasive disease.¹⁰ Women diagnosed with HSIL-CIN 2 typically undergo surgical excision procedures such as a loop electrosurgical excision procedure (LEEP), cold knife conization, or CO₂ laser conization.⁵

Surgical treatment is effective in removing dysplastic tissue. Yet, it does not eradicate the underlying HPV infection.^{7 8} Viral particles can persist in the basal epithelial layers of the transformation zone or be reintroduced via reinfection from sexual partners.^{3 7} As a result, recurrence rates remain considerable, ranging from 5% to 30% within 2 years depending on patient characteristics, surgical margins, HPV genotype, and immune competence.^{5 9}

HPV vaccination has revolutionized primary prevention by inducing high titers of neutralizing antibodies against the L1 capsid protein, thereby blocking infection.^{7 8} The quadrivalent vaccine (Gardasil®) targets HPV types 6, 11, 16, and 18, while the nonavalent formulation (Gardasil 9®) extends protection to five additional oncogenic types.^{7 8} Although initially intended for use before sexual debut,³ growing evidence suggests that HPV vaccination may also play a role in secondary prevention, particularly when administered after surgical treatment of precancerous lesions.^{1 2 4 5 9}

The hypothesized mechanisms include:

- Induction of robust systemic immunity that facilitates clearance of residual HPV particles.^{7 8}
- Prevention of reinfection with vaccine-covered HPV types from sexual partners.³
- Potential cross-protection against phylogenetically related non-vaccine HPV types (e.g., HPV 31, 33, 45).⁷

Recent observational studies and meta-analyses have supported this hypothesis. For example, Del Pino et al. (2023) demonstrated that postoperative vaccination reduced recurrence rates of cervical intraepithelial neoplasia,¹ while Brzeziński et al. (2023) reported a 57% risk reduction.² Meta-analyses by Arbyn et al. (2020) and Nasioutziki et al. (2020) similarly confirmed a protective effect.^{4 9} These findings have prompted international discussions on whether postoperative vaccination should be routinely incorporated into management guidelines.⁵

Given the absence of national HPV vaccination programs in Georgia during the study period and the limited availability of prospective cohort data from the Caucasus region, our study sought to evaluate the effect of postoperative quadrivalent HPV vaccination in preventing HPV reinfection and recurrence after CO₂ laser conization for HSIL-CIN 2 in Georgian women of reproductive age.

Methods

Study Design and Setting: This was a prospective cohort study conducted between January 2019 and December 2023 in two tertiary gynecologic centers in Tbilisi, Georgia: Caraps Medline Clinic and the Georgian-German Reproductive Center. Both centers serve as referral institutions for the management of cervical precancerous lesions.⁶

Ethical approval was obtained from the institutional review boards of both centers, and all participants provided written informed consent.

Study Population: A total of 145 women aged 20-45 years were enrolled. All had histologically confirmed HSIL-CIN 2 and tested positive for high-risk HPV DNA by PCR (types 6, 11, 16, 18, or 31).⁷

Inclusion criteria:

- Age 20-45 years
- Histologically confirmed HSIL-CIN 2
- High-risk HPV PCR positivity
- No prior HPV vaccination⁷

Exclusion criteria:

- Pregnancy at the time of enrollment
- Immunosuppressive conditions (e.g., HIV, chronic corticosteroid use)
- Prior radical cervical surgery or invasive cervical cancer⁶
- Known allergy to HPV vaccine components⁷

Surgical Intervention: All patients underwent CO₂ laser conization combined with vaporization under colposcopic guidance.⁵ Conization specimens were sent for histopathologic evaluation, with margin status documented.

Vaccination Protocol: The intervention group (n = 53) received the quadrivalent HPV vaccine (Gardasil®) within 14 days after surgery, following the standard 0-2-6 month schedule.⁷ Vaccination was offered free of charge through a study support program.

The control group (n = 92) declined vaccination, mainly due to lack of insurance coverage or personal preference.

Follow-Up Assessments: Patients were followed at 3, 6, 9, and 12 months postoperatively.⁷ Each visit included:

- Pap smear cytology interpreted using the Bethesda system.⁶
- Colposcopic examination scored using Reid's colposcopic index.⁶
- HPV DNA PCR testing for types 6, 11, 16, 18, and 31.⁷
- Histologic biopsy with p16 immunohistochemistry when cytologic or colposcopic abnormalities were present.⁵

Definition of recurrence: Either histologically confirmed LSIL/HSIL or persistent HPV DNA positivity with concurrent abnormal cytology.^{4 9}

Laboratory Procedures: HPV DNA was extracted from cervical swab samples and amplified via PCR targeting L1 region-specific primers.⁷ Positive samples were genotyped for HPV types 6, 11, 16, 18, and 31. Immunohistochemistry for p16 was performed using CINtec® p16 histology kit.⁵

Statistical Analysis: Data were analyzed using SPSS v.26. Recurrence-free survival was evaluated using Kaplan-Meier curves with log-rank tests. Cox regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: The mean age was 32.6 years (range 20-45). No significant differences were noted between vaccinated and unvaccinated groups in terms of age, smoking status, parity, baseline HPV genotype, or margin positivity.⁵

Recurrence Rates: At 3 months, recurrence rates were similar between groups (vaccinated 3.8% vs. unvaccinated 5.4%, $p = 0.65$). Divergence emerged by 6 months:

- 6 months: Vaccinated 5.7% vs. unvaccinated 15.2% ($p = 0.04$)
- 9 months: Vaccinated 7.5% vs. unvaccinated 21.7% ($p = 0.02$)
- 12 months: Vaccinated 9.4% vs. unvaccinated 25.0% ($p = 0.01$)

Overall, recurrence-free survival at 12 months was 90.6% in the vaccinated group versus 75.0% in the unvaccinated group. Kaplan-Meier survival analysis confirmed significantly higher recurrence-free survival in vaccinated women (HR 0.41, 95% CI 0.20-0.85).^{1 2 5 9}

HPV DNA Positivity: By 12 months, HPV DNA positivity was observed in 11.3% of vaccinated women compared with 28.3% of unvaccinated women ($p = 0.01$).

Cytological Findings: Cytological abnormalities (ASC-US or higher) were lower among vaccinated patients at all time points. At 12 months, abnormal cytology was observed in 13.2% of vaccinated patients compared with 30.4% of unvaccinated patients.^{1 2 5}

Subgroup Analysis

- Smoking status: Smokers in the unvaccinated group had particularly high recurrence rates (29.6%) compared with nonsmokers (21.2%). In vaccinated women, smoking did not significantly affect recurrence rates.⁵
- Margin status: Women with negative surgical margins still benefited from vaccination, with recurrence rates of 7.8% versus 20.4% in unvaccinated counterparts.⁵

Discussion

Our prospective cohort study demonstrates that administration of the quadrivalent HPV vaccine within 14 days after CO₂ laser conization for HSIL-CIN 2 significantly reduces recurrence of HPV infection and associated cytological abnormalities. Vaccinated women experienced nearly a 60% reduction in recurrence risk over 12 months, consistent with previous studies from other populations.^{1 2 5 9}

Comparison with Previous Literature: Our findings echo those of Ghelardi et al. (2018), who conducted a randomized controlled trial showing a 46% reduction in recurrence with HPV vaccination after CIN 2+ treatment.⁵ Brzeziński et al. (2023) reported a 57% reduction in recurrence,² while Del Pino et al. (2023) confirmed lower recurrence risk in a Spanish cohort.¹ A meta-analysis by Arbyn et al. (2020) estimated an overall 60% reduction in recurrence following vaccination.⁹

Mechanisms of Protection: Possible mechanisms include:

1. Immune clearance of residual virus – vaccine-induced neutralizing antibodies may aid the immune system in eliminating viral particles.^{7 8}
2. Prevention of reinfection – vaccination reduces the risk of acquiring new infections from sexual partners.³
3. Cross-protection – the quadrivalent vaccine may offer protection against genetically related high-risk types, such as HPV 31.⁷

Clinical Implications: Routine postoperative HPV vaccination could transform management of HSIL-CIN 2 by reducing repeat surgical procedures, improving quality of life, and lowering healthcare costs. It aligns with WHO's strategy for cervical cancer elimination.⁶

Fertility Considerations: Vaccination can reduce the need for repeat conization, thereby preserving fertility and lowering obstetric risks.⁵

Limitations: Non-randomized design, 12-month follow-up, quadrivalent vaccine only, and geographic specificity limit generalizability.

Future Directions: Future studies should include longer randomized controlled trials, cost-effectiveness analysis, and assessment of nonavalent vaccines.^{3 7 8}

Conclusion

Postoperative HPV vaccination with Gardasil® in reproductive-age women undergoing CO₂ laser conization for HSIL-CIN 2 significantly reduces recurrence risk, HPV DNA positivity, and abnormal cytology rates.^{1 2 5 9} The protective effect observed in our study is consistent with international evidence, supporting the integration of vaccination into standard postoperative care.^{5 6} Adopting this strategy has the potential to reduce cervical cancer incidence, decrease healthcare costs, and preserve fertility in young women.^{7 8 10}

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ALLERGIES DURING PREGNANCY: RISKS, MANAGEMENT, AND PREVENTION

BIDZINA KULUMBEGOV, MD, PhD

Center of Allergy and Immunology, Tbilisi, Georgia

ABSTRACT

Pregnancy introduces a complex interplay of physiological and immunological adaptations that significantly influence the course of allergic diseases. This review article synthesizes current understanding of allergies during gestation, focusing on its prevalence, the unique risks posed to both mother and fetus, and evidence-based strategies for diagnosis, management, and prevention. The maternal immune system undergoes a crucial shift towards a Th2-dominant state, essential for fetal tolerance but potentially exacerbating allergic manifestations. Hormonal fluctuations further modulate immune responses, contributing to variable disease courses. Uncontrolled allergic conditions, particularly asthma, are associated with substantial maternal complications such as preeclampsia and increased rates of cesarean delivery, and adverse fetal outcomes including hypoxia, preterm birth, and low birth weight. Diagnosis in pregnancy prioritizes fetal safety, favoring in vitro methods over skin or provocation tests. Management emphasizes a multidisciplinary approach, combining non-pharmacological interventions with carefully selected pharmacotherapies, where the risks of uncontrolled disease generally outweigh those of appropriate medication.

Keywords: pregnancy; asthma; allergic rhinitis; food allergy; atopic dermatitis; maternal-fetal health; immunological changes; fetal immune programming; anaphylaxis

Introduction

Allergies represent a significant global health concern, with a rising prevalence affecting over a billion individuals worldwide, particularly young adults. Sensitization rates to common environmental allergens among schoolchildren are approaching 40-50% globally. In the United States, allergic rhinitis impacts between 10% and 30% of the population, food allergies affect 5-8%, and eczema is reported in approximately 10.8% of children.^{1,2,3}

The physiological and immunological changes inherent to pregnancy introduce a unique dynamic for individuals with pre-existing allergies, and can even lead to new-onset symptoms. The trajectory of allergic conditions during pregnancy is highly variable;⁴ approximately one-

third of pregnant individuals experience a worsening of their allergy symptoms, another third find their symptoms remain unchanged, and the remaining third report an improvement. Food allergies are notably common in pregnant women, affecting approximately 20% of pregnant women. Asthma, complicating 3-8.4% of pregnancies, stands as one of the most prevalent chronic medical conditions during gestation. Similarly, allergic rhinitis impacts a substantial proportion of pregnant individuals, with reported incidences around 25% in some studies and a prevalence ranging from 18-30% for all types of rhinitis during pregnancy. Atopic dermatitis is recognized as the most common dermatosis observed during pregnancy.^{5,6,7,8}

Effective management of allergic conditions during pregnancy is paramount for ensuring the well-being of both the pregnant individual and the developing fetus. Uncontrolled allergic diseases, particularly asthma, pose significant risks, including decreased oxygen supply to the fetus, impaired fetal growth, preterm birth, low birth weight, preeclampsia, and increased rates of cesarean delivery.⁹ A critical principle guiding clinical practice is that the potential risks associated with uncontrolled allergic disease generally outweigh the risks posed by appropriate pharmacological interventions. This underscores the necessity for continuous and nuanced management to achieve optimal maternal health and mitigate adverse perinatal outcomes.^{10,11}

Pregnancy necessitates profound adaptations within the maternal immune system. These adaptations are crucial for protecting the pregnant individual and the developing fetus from pathogens while simultaneously maintaining immunological tolerance towards the semi-allogeneic fetus. This intricate balance involves a significant shift in the immune system's phenotype, notably towards a T helper 2 (Th2)-dominant response, which, while vital for fetal tolerance, can also contribute to the exacerbation of allergic reactions. Furthermore, the dramatic fluctuations in pregnancy hormones, particularly estrogen and progesterone, exert a profound influence on immune cell function and can directly modulate the manifestation of allergic diseases. Understanding these physiological and immunological shifts is fundamental to comprehending the unique challenges and considerations in managing allergies during pregnancy.^{12,13,14,15}

Physiological and Immunological Adaptations in Pregnancy and Allergic Responses

The physiological and immunological landscape of pregnancy is meticulously orchestrated to support fetal development while safeguarding maternal health. These adaptations, however, can profoundly influence the manifestation and severity of allergic diseases.¹³

Maternal Immune System Shift (Th1/Th2 Balance, Treg cells)

Normal pregnancy is characterized by a dynamic shift in the maternal immune system. Initially, a transient pro-inflammatory T helper 1 (Th1)-dominant state is observed during the peri-implantation period, which is beneficial for trophoblast invasion. However, this quickly transitions to a predominant T helper 2 (Th2)-dominant anti-inflammatory immune response following placental implantation. This Th2 dominance is crucial for maintaining tolerance towards the semi-allogeneic fetus, preventing its immunological rejection by the maternal immune system. Key cytokines such as interleukin (IL)-4, IL-10, and IL-13 mediate this shift, actively promoting maternal-fetal tolerance and repressing the potentially detrimental Th1 and Th17 immunities. Concurrently, regulatory T cells (Tregs) undergo significant expansion,

particularly at the feto-maternal interface, playing a major role in inducing and maintaining this state of tolerance.^{14,15,16,17,18}

Hormonal Influences (Estrogen, Progesterone) on Immune Cells, IgE Production, and Mast Cell Activity

Pregnancy hormones, most notably estrogen and progesterone, exert a profound and multifaceted influence on the maternal immune system and the course of allergic diseases.

Estrogen, for instance, enhances allergic sensitization. It promotes the differentiation of T helper cells towards a Th2 phenotype, increases the production of immunoglobulin E (IgE), and induces the degranulation of mast cells and basophils, which are key effector cells in immediate hypersensitivity reactions. Estrogen can also augment the function of antigen-presenting cells, further directing the immune response towards a Th2-dominant profile.^{17,18}

Progesterone plays a critical role in maintaining pregnancy by facilitating endometrial changes necessary for implantation and by modulating maternal immune responses to prevent fetal rejection. It possesses anti-inflammatory properties and can regulate T-lymphocyte-mediated immune responses, promoting a Th2-type immunity and suppressing the production of pro-inflammatory Th1 and Th17 cytokines. Progesterone can also inhibit the maturation and T cell-activating capacity of dendritic cells, thereby fostering a state of immune tolerance.^{19,20}

However, the role of progesterone in allergic responses is complex and, at times, appears contradictory. While some studies suggest progesterone inhibits mast cell secretion, others have noted its potential to stimulate IgE-mast cell degranulation. This highlights that progesterone's influence is not uniformly suppressive but rather highly nuanced, likely depending on specific cellular contexts, concentrations, and interactions with other factors. This complexity is further underscored by conditions like Progesterone Hypersensitivity (PH), also known as Autoimmune Progesterone Dermatitis (APD). This rare condition, characterized by symptoms such as dermatitis, urticaria, asthma, and even anaphylaxis, can be triggered by endogenous progesterone or exogenous progestins. It is hypothesized that in susceptible individuals, IgE antibodies may form against progestins, leading to allergic reactions. The occurrence of such hypersensitivity reactions, despite progesterone's overall immune-tolerant role, demonstrates the intricate and sometimes unpredictable nature of hormonal immunomodulation during pregnancy. This makes predicting an individual's allergic response during pregnancy challenging.^{18,20,21}

Other Physiological Changes Impacting Allergic Manifestations

Beyond direct immune cell modulation, other systemic physiological changes during pregnancy can significantly influence the presentation and severity of allergic symptoms.

The nasal mucosa, for instance, undergoes notable changes. Pregnant individuals are frequently prone to nasal blockage, irritating nasal symptoms, and increased nasal discharge, a condition often referred to as "pregnancy rhinitis". Hormonal fluctuations primarily trigger this non-allergic congestion and can mimic the symptoms of a common cold or allergic rhinitis. Typically, pregnancy rhinitis commences in the second trimester and resolves spontaneously within two weeks postpartum. This physiological phenomenon means that nasal symptoms experienced during pregnancy are not always indicative of an allergic exacerbation. Distinguishing between true allergic rhinitis and pregnancy rhinitis is crucial for appropriate diagnosis and management, as treatment approaches may differ.^{21,22}

Changes in the respiratory system, such as an increased tidal volume and altered drug metab-

olism due to increased blood volume, can further complicate the management of conditions like asthma. The vascular system also undergoes significant adaptations; pregnancy is a hypercoagulable state, increasing the risk for deep vein thrombosis. Interactions between acute-phase proteins, the coagulation cascade, and the complement system can influence broader inflammatory responses. Furthermore, there is a gradual and marked increase in neutrophil count from the first trimester onwards, with an elevated basal oxidative burst and increased Neutrophil Extracellular Trap (NET) formation.²³ However, the function of these neutrophils may be decreased after activation, presenting a complex picture of innate immune activity. These systemic changes are not merely incidental; they actively modify how allergic symptoms manifest and are managed. This underscores the need for careful clinical assessment that extends beyond simple allergy testing to distinguish true allergic exacerbations from physiological changes of pregnancy, as treatment strategies may differ.²¹

Risks and Maternal-Fetal Outcomes of Allergies During Pregnancy

Allergic conditions during pregnancy carry distinct risks that can impact both the pregnant individual and the developing fetus. The severity and nature of these risks vary depending on the specific allergic disease and its level of control.

General Allergic Reactions (Anaphylaxis)

Anaphylaxis, a severe, potentially life-threatening systemic allergic reaction, is rare during pregnancy, with an estimated frequency between 1.5 to 3.8 per 100,000 pregnancies. Despite its rarity, it poses significant risks to both the pregnant individual and the fetus. Anaphylaxis-related maternal mortality is estimated at 0.05 per 100,000 live births. The primary triggers identified in pregnant individuals include beta-lactam antibiotics (58% of cases), latex (25%), and anesthetic agents (17%), with a notable proportion (49-74%) of cases occurring during cesarean sections. Management of anaphylaxis in pregnancy generally mirrors that in non-pregnant patients, with epinephrine being the recommended first-line treatment due to its critical role in reversing severe symptoms and its established safety profile in this context. Risk factors for anaphylaxis during pregnancy include a history of multiple cesarean sections or other procedures, a personal history of anaphylaxis, or previous allergic reactions to medication without a proper allergy work-up.^{24,25,26}

Asthma

Asthma is one of the most common medical concerns complicating pregnancy, affecting 4-8% of gestations. The course of asthma during pregnancy is highly variable; approximately one-third of individuals experience a worsening of symptoms, often in the late second and early third trimesters, while another third see improvement, and the remaining third report no change. Severe asthma is more prone to exacerbation during pregnancy.²⁷

Maternal Risks: Poorly controlled asthma in pregnancy is associated with several adverse maternal outcomes. There is an increased risk of preeclampsia, with some studies reporting up to a 54% increased risk. Other complications include a 34% increased odds of hemorrhage during pregnancy and a 52% increased odds of premature contractions. The rate of cesarean delivery is also significantly increased in individuals with asthma (odds ratio 1.32). Severe and inadequately managed asthma can further lead to increased maternal morbidity and, in rare cases, mortality.^{27,28}

Fetal Risks: The impact of uncontrolled maternal asthma on fetal health is substantial. Asthma exacerbations can lead to decreased oxygen levels in the mother's blood, which directly reduces the oxygen supply to the fetus, thereby impairing healthy fetal growth and development. This physiological consequence is a primary driver of adverse fetal outcomes, including a 41% higher risk of preterm birth, a 46% increased risk of low birth weight, and a 22% increased risk of infants being small for gestational age. Infants born to mothers with uncontrolled asthma also face increased perinatal morbidity, including a higher incidence of respiratory distress syndrome (RDS) and an elevated need for neonatal intensive care unit (NICU) admission. Furthermore, there is a small but statistically significant increased risk of overall congenital malformations (relative risk 1.11), with a specific heightened risk of cleft lip with or without cleft palate (relative risk 1.30). An increased risk of perinatal mortality (relative risk 1.25) has also been reported in infants of asthmatic mothers.^{29, 30}

Allergic Rhinitis (including Pregnancy Rhinitis)

Allergic rhinitis is common among pregnant individuals, with 10-30% of adults affected globally and 10-30% of women experiencing symptom worsening during pregnancy. Pregnancy rhinitis, a non-allergic nasal congestion, affects 9-39% of pregnant individuals, typically appearing in the second or third trimester and resolving postpartum.^{31,32}

Maternal Risks: Severe symptoms of allergic rhinitis can significantly impair maternal eating, sleeping, and emotional well-being. Uncontrolled rhinitis may predispose individuals to sinusitis or worsen co-existing asthma. Persistent nasal obstruction, whether allergic or pregnancy-induced, can lead to reduced sleep quality, snoring, and obstructive sleep apnea (OSA).

Fetal Risks: While direct fetal risks specifically from allergic rhinitis are less definitively established compared to asthma, severe nasal congestion, particularly if leading to chronic maternal hypoxia or fragmented rest, *may* be associated with adverse perinatal outcomes. These include gestational hypertension, intrauterine growth retardation, preeclampsia, and lower Apgar scores in neonates. However, some studies have unexpectedly suggested that allergic rhinitis may offer a protective effect against unfavorable pregnancy outcomes, highlighting the need for further research in this area.^{33,34,35}

Food Allergies

Food allergies are more prevalent in pregnant individuals, affecting approximately one in five. These allergies can manifest at any point during pregnancy, with symptoms typically appearing immediately or within a few hours of allergen ingestion. Common food allergens include seafood, milk, eggs, peanuts, tree nuts, wheat, and soy.³⁶

Maternal Risks: Food allergies can profoundly impact maternal health, leading to a range of symptoms such as rash, hives, vomiting, stomach cramps, diarrhea, and angioedema. Severe allergic reactions, including anaphylaxis, carry the risk of serious obstetric complications such as miscarriage or premature birth.

Fetal Risks: Maternal allergies during pregnancy are believed to increase the risk of the child developing allergies post-birth. The underlying allergic mechanisms may potentially hinder fetal growth and development or directly affect the developing fetal lungs and bronchi, raising concerns about potential birth defects. However, the precise reasons and evidence for the causes of new-onset food allergies during pregnancy and their direct impact on fetal development require further exploration.^{37,38}

Atopic Dermatitis (Eczema)

Atopic dermatitis (AD), or eczema, is the most common dermatosis encountered during pregnancy. Its course is often fluctuating; approximately 25% of pregnant individuals experience an improvement in symptoms, while over 50% report a deterioration, with a slightly higher rate of worsening observed in the second trimester. About 10% of cases may flare in the postpartum period. New onset of AD symptoms during pregnancy is also common, occurring in 60-80% of cases.^{39, 40}

Table 1. Summary of Maternal and Fetal Risks Associated with Allergic Conditions in Pregnancy

Allergic Condition	Maternal Risks	Fetal/Offspring Risks	Key Quantitative Data
Anaphylaxis	Rare, but life-threatening; risk to mother and fetus; can cause miscarriage/premature birth.	Fetal distress, hypoxia, and potential mortality	Frequency: 1.5-3.8 per 100,000 pregnancies; Maternal mortality: 0.05 per 100,000 live births
Asthma	Preeclampsia, hemorrhage, premature contractions, increased C-section rates, maternal morbidity/mortality	Hypoxia, impaired fetal growth, preterm birth, low birth weight, small for gestational age (SGA), respiratory distress syndrome (RDS), NICU admission, congenital malformations (cleft lip/palate), perinatal mortality	Preeclampsia: up to 54% increased risk; Hemorrhage: 34% increased odds; Preterm contractions: 52% increased odds; C-section: OR 1.32; Preterm birth: 41% higher risk; Low birth weight: 46% increased risk; SGA: 22% increased risk; Congenital malformations: RR 1.11; Cleft lip/palate: RR 1.30; Perinatal mortality: RR 1.25
Allergic Rhinitis (including Pregnancy Rhinitis)	Impaired eating/sleeping, emotional distress, sinusitis, worsening asthma, obstructive sleep apnea (OSA)	Potential association with gestational hypertension, intrauterine growth retardation, preeclampsia, and lower Apgar scores (due to chronic maternal hypoxia from nasal congestion). Some studies suggest a protective effect against unfavorable pregnancy outcomes.	Prevalence: 18-30% (all rhinitis), 9-39% (pregnancy rhinitis)

Allergic Condition	Maternal Risks	Fetal/Offspring Risks	Key Quantitative Data
Food Allergies	Rash, hives, vomiting, diarrhea, angioedema, anaphylaxis, miscarriage, premature birth	Increased offspring allergy risk, hindered fetal growth/development, potential damage to fetal lungs/bronchi, and potential birth defects.	Affects ~1 in 5 pregnant women
Atopic Dermatitis (Eczema)	Impact on quality of life, bacterial/herpetic infections, anxiety, mood changes, depression	No direct harm, but increased offspring eczema risk if parental history; altered in utero growth patterns, premature rupture of membranes, staphylococcal neonatal septicemia, link to maternal stress	Most common dermatosis of pregnancy ; >50% experience deterioration

Diagnosis of Allergies in Pregnancy

Accurate diagnosis of allergic conditions during pregnancy is crucial for effective management and to differentiate allergic symptoms from physiological changes unique to gestation.

Preferred Diagnostic Methods (in vitro tests for IgE) and Limitations of Others (skin/provocation tests)

When diagnosing allergies in pregnant individuals, *in vitro* diagnostic methods are generally preferred due to safety considerations associated with direct allergen exposure. Serological tests for allergen-specific IgE, such as Immuno-CAP or RAST or lymphocyte transformation tests for type IV allergy diagnosis, are recommended. These methods allow for the detection of allergen sensitization without exposing the pregnant individual or fetus to the allergen itself.^{41, 42, 43} Conversely, skin prick tests and provocation tests are typically deferred until after birth. This cautious approach stems from the small, though finite, risk of inducing a systemic allergic reaction, including anaphylaxis, during these procedures. Any systemic reaction, particularly anaphylaxis, poses a direct risk to the fetus due to potential maternal hypoxia and subsequent reduced oxygen supply to the fetus. Therefore, the preference for *in vitro* tests, which avoid direct allergen exposure to the mother, reflects a fundamental principle in pregnancy care: minimizing any iatrogenic risk to the fetus, even if low, by opting for safer diagnostic alternatives when available. Similarly, patch testing is generally advised against as a general precaution, even though no documented adverse effects exist, because test findings can interfere with the immunological changes induced by pregnancy.^{44, 45, 46}

Management of Allergies During Pregnancy

Effective management of allergies during pregnancy is crucial for mitigating risks to both the pregnant individual and the fetus. This requires a balanced approach, prioritizing symptom control while minimizing the potential adverse effects of interventions.^{47, 48}

General Principles

Management of allergic conditions in pregnancy necessitates a nuanced, individualized, and often multidisciplinary approach involving collaboration among allergists, obstetricians, and dermatologists. A guiding principle for pharmacological interventions is to use the “lowest effective dose for the shortest duration necessary” to control symptoms. Regular monitoring of clinical symptoms is essential, with monthly evaluations specifically recommended for asthma to track disease course and adjust treatment as needed.^{49, 50}

Pharmacological Interventions

Pharmacological interventions are often necessary to achieve adequate symptom control and prevent complications, with careful consideration given to fetal safety.

Antihistamines: Second-generation non-sedating antihistamines such as loratadine and cetirizine are generally preferred during pregnancy due to their excellent safety records and no significant increase in congenital malformations, even when used in the first trimester. While they can be used throughout pregnancy, it is generally recommended to start them after the first trimester if possible. First-generation antihistamines like chlorpheniramine and diphenhydramine have a long history of use with reassuring animal studies. Still, their sedative properties are a significant drawback, impacting maternal performance and well-being. Chlorpheniramine is often considered the preferred sedating option when needed. Antihistamines with limited human pregnancy data, such as acrivastine and fexofenadine, should be used with caution, with fexofenadine reserved for cases where no other suitable treatment is available.^{51,52,53,54}

Corticosteroids:

- **Inhaled Corticosteroids (ICS):** These are the first-line controller therapy for persistent asthma. Budesonide is the preferred ICS during pregnancy due to extensive safety data, but other ICS agents (e.g., fluticasone) can be safely continued if they were effective prior to conception.^{54,55}
- **Intranasal Corticosteroids (INCS):** Considered the most effective treatment for allergic rhinitis. Budesonide is the INCS of choice, while fluticasone and mometasone are also considered safe options. Triamcinolone and beclomethasone should be avoided due to potential teratogenic effects or inferiority.⁵⁶
- **Topical Corticosteroids (for Eczema):** Mild to moderate potency topical corticosteroids (e.g., hydrocortisone, triamcinolone, mometasone) are generally safe and preferred, used at the lowest effective dose for the shortest duration necessary to control symptoms.
- **Oral Corticosteroids:** These are not preferred for regular, long-term treatment but can be used for severe asthma attacks or acute eczema flares when the benefits clearly outweigh the risks.^{57,58,59}

Immunotherapy (Allergy Shots): If a pregnant individual is already receiving allergen immunotherapy and becomes pregnant, maintenance treatment can generally be continued safely, but the allergen dose should not be increased. However, it is generally not recommended to *initiate* immunotherapy during pregnancy due to the risk of systemic reactions (anaphylaxis) with increasing doses and the delay in achieving effectiveness. In very high-risk situations, such as Hymenoptera (insect venom) hypersensitivity with a history of anaphylaxis, initiation might be considered after careful risk-benefit assessment.^{60,61}

Emergency Management

For severe allergic reactions like anaphylaxis, immediate treatment with epinephrine is critical and is considered safe and recommended during pregnancy. Individuals with severe allergies should have a completed Anaphylaxis Action Plan and carry epinephrine auto-injectors at all times for immediate use.^{62,63}

Breastfeeding Considerations

Breastfeeding is strongly recommended for its numerous benefits, including enhancing a child's immunity. Medications considered safe for use during pregnancy can generally be continued while nursing, as the amount of medicine transferred to the infant via breast milk is typically less than the exposure *in utero*. For topical eczema treatments, it is advisable to avoid applying medication directly to the nipple area or to clean the area before nursing to minimize infant exposure gently.⁶⁴

Table 2. Recommended Pharmacological Management of Allergic Conditions During Pregnancy

Drug Class	Preferred Agents/ Examples	Safety Profile/ Category	Key Considerations
Antihistamines	Loratadine, Cetirizine (2nd Gen)	Preferred, generally safe; no significant increase in congenital malformations	Non-sedating; generally best taken after 1st trimester if possible
	Chlorpheniramine, Diphenhydramine (1st Gen)	Long history of use, but sedative qualities are a drawback	Sedating: Chlorpheniramine often preferred if sedation is needed
Decongestants	Oral: Pseudoephedrine, Phenylephrine	Generally not recommended; pseudoephedrine linked to a slight increase in abdominal wall defects	Potential for reduced placental blood flow; use in 1st trimester only for severe, unrelieved symptoms
	Nasal Sprays: Oxymetazoline	Appears safest due to minimal systemic absorption	Limit to very intermittent use (≤ 3 days) to avoid rebound congestion
Corticosteroids	Inhaled (ICS): Budesonide	Preferred ICS; extensive safety data	First-line for persistent asthma; others can be continued if effective
	Intranasal (INCS): Budesonide	INCS of choice; Fluticasone, Mometasone, also safe	Most effective for allergic rhinitis; avoid Triamcinolone, Beclomethasone

Drug Class	Preferred Agents/ Examples	Safety Profile/ Category	Key Considerations
	Topical (for Eczema): Hydrocortisone, Desonide, Triamcinolone, Mometasone	Mild to moderate potency preferred, generally safe	Use the lowest effective dose for the shortest duration; very potent associated with low birth weight
	Oral: Prednisone	Not preferred for regular use; for severe attacks only	Use in short bursts; caution in 3rd trimester; IV during labor if on systemic steroids
Leukotriene Receptor Antagonists (LTRAs)	Montelukast	Generally safe; no major teratogenic risk or association with neuropsychiatric events	Potential slight risk of congenital cardiac abnormalities; benefits often outweigh risks
Immunotherapy	Continuation of pre- existing treatment	Generally safe to continue the maintenance dose	Dose should not be increased; do not initiate during pregnancy (anaphylaxis risk)
Biologics	Asthma: Omalizumab, Mepolizumab, Dupilumab, Tezepelumab	Good efficacy, acceptable safety; international consensus for use	Weigh risks vs. benefits; can be initiated/continued throughout pregnancy and breastfeeding
	Atopic Dermatitis: Dupilumab	Probably safe; no significant increase in miscarriage or congenital malformations	Topical calcineurin inhibitors (TCIs) relatively safe; avoid Methotrexate, Mycophenolate mofetil.

Environmental Modifications

Reducing exposure to indoor allergens (e.g., dust mites, pet dander) and outdoor pollutants (e.g., tobacco smoke, volatile organic compounds from new carpets or renovations) is a crucial preventive measure. Maternal smoking during pregnancy is identified as a potent trigger for the development of allergies and asthma in offspring.

Other Preventive Measures

Pre-conception Counseling: Optimizing maternal health and ensuring reasonable control of pre-existing asthma or allergies before conception is considered an ideal preventive strategy.⁶⁵

Mode of Delivery: Studies have indicated an association between cesarean section, particularly elective cesarean delivery, and a higher risk of allergic rhinitis in offspring. This potential link is hypothesized to be due to altered infant microbial diversity compared to vaginal delivery, which influences immune development.^{66,67,68}

Exclusive Breastfeeding: Exclusive breastfeeding for the first 4 to 6 months is recommended, as it can contribute to increasing a child's immunity.⁶⁹

Maternal Psychological Well-being: Maternal stress and depression during pregnancy have been linked to an increased risk of offspring atopic eczema. This suggests that interventions aimed at optimizing maternal mental health and reducing stress could potentially lower the risk of infantile atopic dermatitis.^{70,71}

Conclusion

Pregnancy represents a unique physiological and immunological state that profoundly influences the manifestation and management of allergic diseases. The maternal immune system's essential shift towards a Th2-dominant environment, while critical for fetal tolerance, simultaneously creates a milieu that can exacerbate allergic responses. Hormonal fluctuations further modulate these immune dynamics, leading to a variable course of allergic conditions during gestation.

The implications of uncontrolled allergies during pregnancy are significant, posing substantial risks to both the pregnant individual and the developing fetus. Poorly managed conditions, particularly asthma, can lead to severe maternal complications such as preeclampsia and increased rates of cesarean delivery, and adverse fetal outcomes including hypoxia, preterm birth, and impaired growth. The imperative to maintain adequate fetal oxygenation often dictates that the benefits of appropriate pharmacological management outweigh the risks of medication.^{72,73}

Current diagnostic approaches prioritize fetal safety, advocating for *in vitro* tests over methods involving direct allergen exposure. Management strategies emphasize a multidisciplinary, individualized approach that integrates non-pharmacological interventions with carefully selected pharmacotherapies.^{74,75} A notable evolution in the understanding of offspring allergy prevention has occurred, moving away from the once-common recommendation of maternal dietary allergen avoidance towards encouraging the consumption of common allergens during pregnancy to foster immune tolerance. This shift, alongside the growing evidence for specific nutritional supplements, highlights the dynamic interplay between maternal health and offspring immune development. The concept of fetal immune programming underscores the profound, intergenerational legacy of maternal immune status and environmental exposures on a child's long-term allergy risk.

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ალერგია ორსულობის დროს: რისკები, მართვა და პრევენცია

ბიძინა კულუშბაშვი, მედიცინის დოქტორი

ალერგიისა და იმუნოლოგიის ცენტრი, თბილისი, საქართველო.

აბსტრაქტი

ორსულობა იწვევს ფიზიოლოგიური და იმუნოლოგიური ადაპტაციის რთულ ურთიერთქმედებას, რომელიც მნიშვნელოვნად გავლენას ახდენს ალერგიული დაავადებების მსვლელობაზე. ეს მიმოხილვითი სტატია აღწერს ორსულობის პერიოდში ალერგიის შესახებ არსებულ ცოდნას, ფოკუსირებულს მის გავრცელებაზე და რისკებზე, რომელსაც ის ქმნის როგორც დედისთვის, ასევე ნაყოფისთვის. დედის იმუნური სისტემა განიცდის კრიტიკულ ცვლილებას Th2-დომინანტური მდგომარეობისკენ, რაც აუცილებელია ნაყოფის ტოლერანტობისთვის, მაგრამ შესაძლოა გაძლიერდეს ალერგიული გამოვლინებები. ჰორმონალური ცვლილებები კიდევ უფრო მოდულირებს იმუნურ რეაქციებს, რაც ხელს უწყობს დაავადების ცვალებად მსვლელობას. უკონტროლო ალერგიული მდგომარეობები, განსაკუთრებით ასთმა, ასოცირებულია მნიშვნელოვან გართულებებთან, როგორიცაა პრეეკლამფსია და საკეისრო კვეთის გაზრდილი მაჩვენებლები, ასევე ნაყოფის უარყოფით შედეგებთან, მათ შორის ჰიპოქსია, ნაადრევი მშობიარობა და დაბადების დაბალი წონა. ორსულობის დროს დიაგნოსტიკისას პრიორიტეტი ენიჭება ნაყოფის უსაფრთხოებას, უპირატესია ინ ვიტრო მეთოდები, ვიდრე კანის ან პროვოკაციული ტესტები. ალერგიული ორსულის მართვა ხაზს უსვამს მულტიდისციპლინური მიდგომის აუცილებლობას, აერთიანებს არაფარმაკოლოგიურ ინტერვენციებს და ყურადღებით შერჩეულ მედიკამენტებს.

საკვანძო სიტყვები: ორსულობა, ასთმა, ალერგიული რინიტი, საკვების ალერგია, ატოპური დერმატიტი, დედა-ნაყოფის ჯანმრთელობა, იმუნოლოგიური ცვლილებები, ანაფილაქსია.

GESTATIONAL DIABETES MELLITUS – FROM RISK FACTORS TO PREVENTION

RAMAZ KURASHVILI, MD, PhD^{1,2,3,4,5}

ELENA SHELESTOVA, MD, PhD^{2,3,4,5}

¹ European University (EU), Department of Endocrinology, Tbilisi, Georgia

² Georgian National University (SEU), Tbilisi, Georgia

³ National Center for Diabetes Research, Tbilisi, Georgia

⁴ Diabetes and Endocrinology Association (DEA-Union), Tbilisi, Georgia

⁵ Noncommunicable Diseases Alliance (NCD-Alliance), Tbilisi, Georgia

ABSTRACT

Gestational diabetes mellitus (GDM) is the most common pregnancy complication globally. GDM prevalence ranges from <3% to >20%. One in 5 livebirths is affected by hyperglycemia in pregnancy (HIP), and 1 in 6 is explicitly affected by GDM. HIP is classified as pregestational diabetes, gestational diabetes, and diabetes in pregnancy. 75%-90% of HIP cases are GDM. Diverse environmental, socioeconomic, and individual risks play a pivotal role in the global rise in GDM. *Environmental risks* affect the gut microbiome, causing oxidative stress, inflammation, insulin resistance, neurohormonal/ β -cell dysfunction, and genetic/epigenetic modification. These factors are associated with an increased risk of GDM and its short-term/long-term complications. A “neglected pollutant” (artificial light/noise) causes significant damage to women’s health. Light pollution (screen light, streetlights, artificial light at night) causes circadian rhythm and sleep disorders that lead to GDM. Mothers with *low socio-economic status* (an index assessing educational level and employment) have an increased risk of GDM. There is a wide range of *individual risks* – reversible (obesity, passive lifestyle, unhealthy diet, smoking, stress, etc) and irreversible (maternal age, family history of DM/GDM, miscarriages/stillbirth in previous pregnancies, etc). The more risk factors a woman has, the higher her risk of GDM. Undiagnosed/untreated GDM is associated with a wide range of maternal complications during pregnancy, labor, postpartum, and beyond, and fetal congenital/neonatal complications. Though GDM is not preventable, its risk can be lowered – the ideal time to influence GDM risks is around pregnancy. Elimination of reversible risks is essential to halt the global rise of GDM. Its screening, treatment, and management reduce feto-maternal morbidity/mortality.

Keywords: gestational diabetes mellitus; environmental and socio-economic risk factors; individual risk factors; feto-maternal outcomes; screening, prevention

გესტაციური შაქრიანი დიაბეტის რისკის ფაქტორებიდან პრევენციამდე

რამაზ ყურაშვილი, MD, PhD^{1,2,3,4,5}; ალენა შელესტოვა MD, PhD, პროფ.^{2,3,4,5}

¹ ევროპული უნივერსიტეტი (EU), ენდოკრინოლოგიის დეპარტამენტი, თბილისი, საქართველო

² საქართველოს ეროვნული უნივერსიტეტი (SEU), თბილისი, საქართველო

³ დიაბეტის ეროვნული კვლევითი ცენტრი, თბილისი, საქართველო

⁴ დიაბეტისა და ენდოკრინოლოგიის ასოციაცია (DEA-Union), თბილისი, საქართველო

⁵ საქართველოს აგდ ალიანსი (NCD-Alliance), თბილისი, საქართველო

აბსტრაქტი

გესტაციური შაქრიანი დიაბეტი (გმდ) მსოფლიოში ორსულობის ყველაზე გავრცელებულ გართულებას წარმოადგენს. მისი გავრცელება <3%-დან >20%-მდე მერყეობს. ორსულობის დროს ჰიპერგლიკემიის ფონზე ყოველი 5 ცოცხლად შობილიდან ერთი ვითარდებოდა, ხოლო კონკრეტულად გმდ-ის ფონზე კი ყოველი 6-დან 1. ორსულობის დროს ჰიპერგლიკემია შემდეგნაირად კლასიფიცირდება: პრეგესტაციური დიაბეტი, გმდ და დიაბეტი, პირველად აღმოჩენილი ორსულობის დროს, გმდ-ზე მოდის შემთხვევათა 75%-90%.

გარემოს, სოციალურ-ეკონომიკური და ინდივიდუალური რისკის ფაქტორები წამყვან როლს თამაშობენ გმდ-ის. გარემოს რისკის ფაქტორები გავლენას ახდენენ ნაწლავის მიკრობიოტაზე, იწვევენ ჟანგვით სტრესს, ანთებას, ინსულინრეზისტენტობას, ნეიროჰორმონალურ/β-უჯრედების დისფუნქციას და გენეტიკურ/ეპიგენეტიკურ მოდიფიკაციას. ეს ყველაფერი ზრდის გმდ-ს და მისი ახლო/შორეული გართულებების განვითარების რისკს. ისეთი “უგულელებლყოფილი დამაბინძურებლები”, რომლებიცაა ხელოვნური სინათლე და ქუჩის ხმაური. მნიშვნელოვან ზიანს აყენებენ ქალის ჯანმრთელობას და დაკავშირებულია გმდ-ის რისკის ზრდასთან. სინათლის დაბინძურება (ეკრანის ნათება და ქუჩის განათება) იწვევს ცირკადული რიტმის და ძილის დარღვევებს, რაც ზრდის გმდ-ის რისკს. დედის დაბალი სოციალურ-ეკონომიკური სტატუსი (განათლების დონეს პლუს დასაქმებას) განაპირობებს გმდ-ის უფრო მაღალ რისკს. ინდივიდუალური რისკები იყოფა შექცევად (მაგ. სიმსუქნე, პასიური ცხოვრების წესი, არაჯანსაღი კვების ჩვევები, მოწევა, სტრესი და ა.შ.) და შეუქცევად (დედის ასაკი, დიაბეტის ოჯახური ისტორია, გესტაციური დიაბეტი ანამნეზში, ჩვეული აბორტები და მკვდრად შობადობა წინა ორსულობებში და ა.შ.) ფაქტორებად. რაც უფრო მეტი რისკის ფაქტორი აქვს ქალს, მით უფრო მაღალია გმდ-ის განვითარების რისკი. ამგვარად, გესტაციური დიაბეტის სკრინინგი, მკურნალობა და მართვა აუცილებელია და მიზნად ისახავს ორსულობის ცუდი შედეგების თავიდან აცილებას. მიუხედავად იმისა, რომ გმდ-ის სრული პრევენცია არ შეიძლება, არსებობს რისკის შემცირების სხვადასხვა გზა.

დასკვნა: გმდ-ს რისკის ფაქტორების აღმოფხვრა მნიშვნელოვანია მისი გავრცელების ზრდის შესაჩერებლად. არადიაგნოსტირებული გმდ, ანდ გმდ, რომლის დიაგნოზი არ იყო დასმული დროულად, არ იყო ნამკურნალები, საგრძნობლად ზრდის ნაყოფისა და დედის ავადობასა და სიკვდილიანობას.

საკვანძო სიტყვები: გესტაციური შაქრიანი დიაბეტი; გარემო და სოციალურ-ეკონომიკური რისკის ფაქტორები; ინდივიდუალური რისკის ფაქტორები; ნაყოფისა და დედის გამოსავლები; სკრინინგი; პრევენცია

Introduction

According to the UNO and WHO, four basic non-communicable diseases (NCDs) are: cardiovascular diseases (CVD), diabetes mellitus (DM), including gestational diabetes (GDM), cancer, and chronic respiratory diseases. All NCDs are programmed and imprinted during pregnancy. Thus, hyperglycemia during pregnancy can change fetal programming with metabolic complications in adult life! GDM is one of the three main types of DM, it is one of the most common complications during pregnancy globally. One in 5 live births is affected by hyperglycemia in pregnancy, and 1 in 6 is explicitly affected by GDM. Its prevalence varies from less than 3% (Norway/2% and Sweden/2.5%) to more than 20% (Spain/37.6%, Malaysia/27.3%, Thailand/26.5%, Germany/26.1%, India/26.1%, UK/23.1%, South Korea/21%, Vietnam/21%).^{1,4}

Classification

According to the WHO and the International Federation of Gynaecology and Obstetrics (FIGO)/ International Diabetes Federation (IDF) Joint Statement (2018), hyperglycaemia in pregnancy (HIP) can be classified as pregestational diabetes, gestational diabetes (GDM), or diabetes in pregnancy (DIP).^{2,3} Pre-gestational diabetes is type 1, type 2, or other rarer forms of diabetes that were diagnosed in pregnant women before conception. DIP is hyperglycaemia first diagnosed during pregnancy, meeting the WHO criteria of diabetes in non-pregnant women.⁴ Available data indicate that 75% to 90% of HIP cases are GDM, which occurs in 2-10% of all pregnancies (Tables 1 and 2).⁴

Table 1. Global estimates of hyperglycemia in pregnancy in 2024 (total live births to women aged 20-49 years in millions)

Hyperglycemia in pregnancy	
Global prevalence	19.7%
Number of live births affected in millions	23.3 million
Proportion of cases due to GDM	79.2%
Proportion of cases due to diabetes (T1/T2) first detected in pregnancy	9.9%
Proportion of cases due to diabetes detected prior to pregnancy	11%

Table 2. Hyperglycemia in pregnancy in the European region in 2024 (total live births to women aged 20-49 years in millions)

Age-adjusted prevalence (%)	Raw prevalence (%)	Number of live births affected in millions
14.2	15.9	1.5

GDM may occur at any time during pregnancy and, generally, disappears after the baby is born. However, the risk of developing T2DM in future life or GDM in subsequent pregnancies remains very high.

What Is GDM?

The World Health Organization (WHO) defines GDM as “any level of the early or first detection of glucose intolerance in pregnancy”. Gestational diabetes mellitus (GDM) is a non-communicable disease affecting pregnant women. It is a condition in which human placental lactogen (HPL) prevents the body from using insulin effectively. It leads to hyperglycemia and gestational diabetes. GDM is a condition in which a woman without diabetes develops high blood sugar levels, which is first diagnosed during pregnancy and generally resolves at birth.

There are two types of GDM, which are categorized based on the treatment required to keep blood sugar levels in an optimum range:

- A1GDM - known as “diet-controlled gestational diabetes” (it can be managed without medication), and
- A2GDM - this type needs to be treated with medicine.⁵

Although the cause of GDM is not known, there are some theories as to why the condition occurs. And risk factors, without doubt, play an important role.

What Are the Risk Factors Associated with GDM?

The environmental, socioeconomic, and individual risk factors associated with GDM play a pivotal role, causing a constant global rise in GDM prevalence over the past two decades.⁶

GDM and Environmental Risk Factors

Experimental studies suggested that the potential biological mechanisms of environmental pollutants, such as ratio of grey space-to-green space, buildings and city planning, walking and recreation spaces; food environment; soil and water pollution, air pollution with, such pollutants as oxinitrides - NOX, NO, NO₂; CO, SO₂, O₃; climate factors, such as seasons or very high ambient temperature in spring and summer and hot weather; chemicals and metals (methyl mercury, cadmium, tributylene, arsenic, phthalates, phenols, titanium dioxide/TiO₂, mercury/methylmercury) in sea food; persistent organic pollutants (pesticides, industrial chemicals, etc) all affect gut microbiom, cause oxidative stress, inflammation, insulin resistance, neurohormonal and β-cell dysfunction, and epigenetic modification. All this might be associated with an increased risk of GDM and its short-term and long-term complications.⁷

Bisphenol A (BPA) is an endocrine-disruptor that is used in the production of polycarbonate plastics. There is evidence that maternal exposure to BPA, even among pregnant women of normal weight, is associated with an increased risk of GDM. BPA, and its analogues BPS, BPF, and BPAF, are detected in indoor dust samples and food and beverages, which indicates a constant harmful exposure to bisphenols.⁸⁻¹²

Other “neglected pollutants” that cause significant damage to human health are light (artificial) and noise. High levels of road traffic noise adversely affect 40% of the population. Light pollution (including the use of phones, computers, tablets, and watching TV before going to bed, as well as street lights) may be associated with the increased risk of GDM. A study demonstrates that it causes circadian rhythm and sleep disorders that can disrupt glucose metabolism.¹³

GDM and Socio-Economic Risk Factors

According to results from the Generation R Study, low maternal educational level promoted the development of GDM.¹⁴⁻¹⁵

An Italian study from Turin found that mothers with low socioeconomic position (a composite index assessing educational level and employment) were at a higher risk of developing GDM.¹⁶

GDM and Individual Risk Factors

The leading individual risk factors of GDM are:

- Age ≥35 years, or decreased function of internal organs (in particular, the pancreas)
- High BMI prior pregnancy: overweight (>25 kg/m²) and obesity(>30 kg/m²);
- Gaining too much weight (>10kg) in the 1-st trimester of the current pregnancy;
- Family history of type 2 DM and GDM (in the 1-st-degree relatives);
- Pre-diabetes;

- History of GDM, previous infant with birth weighing >4000 g, previous stillbirth and/or recurrent abortions (>3 in previous pregnancies), fetal malformations, preterm delivery (<37 gestational weeks), Cesarean section, multiple pregnancy (2-3 fetuses);
- HbA1c >5.7;
- Glucosuria in the current pregnancy;
- Abnormal OGTT (oral glucose tolerance tests);
- Dyslipidemia (low HDL-CH,TR >200 mg/dl);
- Hypertension (chronic and pregnancy-induced);
- Conditions associated with insulin resistance - Polycystic Ovary Syndrome (PCOS) and Acanthosis Nigricans;
- Polihydramnio.

Such individual, habitual risk factors as low physical activity, glucocorticoid administration, and smoking play an important role in the development of all non-communicable diseases, including GDM!^{17,18}

Stress of any form has the potential to exacerbate GDM risk independently.¹⁹

Smoking specifically causes insulin resistance, leading to obesity and pre-diabetes, thus aggravating the risk of GDM. It carries triple dan for a:

- woman, especially a pregnant one;
- fetus, and
- future generations.²⁰

The more risk factors a woman has, the higher the risk of developing GDM. In the presence of multiple risk factors, supervision by a multidisciplinary team is required.

It is preferable if supervision is initiated well before conception.

Hyperglycemia in Pregnancy and Maternal Age

Risk of hyperglycemia during pregnancy increases with maternal age, reaching its peak at the age of 45-49 years (42.3%). Since the majority of pregnancies and births occur at <30 years of age (46.3%, or 9.8 million), the majority of cases of hyperglycemia in pregnancy occur in this age group.

One of the meta-analyses, published in 2020, demonstrates that the risk of GDM increases linearly with successive age groups.²¹

However, over the last few decades, there has been an increase in the number of primigravida aged 35 years and older.

Risks Categories of GDM

Risk of GDM development falls into the following three categories:

High Risk:

- Pre-diabetes
- History of GDM
- Long-term (more than three courses/year) steroid use at a daily dose of ≥5mg
- Pre-existing CVD
- Ethnicity
- Obesity (BMI ≥30 kg/m²)
- Waist circumference >80cm females

Moderate Risk:

- Physical inactivity
- Energy-dense Western-style diet
- Smoking

- Family history of DM
- Hypertension
- PCOS
- Metabolically-dysfunction-associated steatotic liver disease (MASLD)
- Low socioeconomic status
- Age >45 years

Low Risk:

- Age <45 years, with absence of any of the above

GDM and Conditions That Increase the Risk of fGDM

Duration and Quality of Sleep

Evidence demonstrates that sleep disorders may increase pregnancy complications, including GDM. Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing. It was shown that OAS increases the risk of GDM. Short and long sleep durations have also been linked to GDM. An association between poor sleep quality and GDM has been observed; however, it remains unclear whether improved sleep duration and/or quality will lead to improved glucose metabolism.²²⁻²⁴

Vitamin D Deficiency

Vitamin D deficiency has been increasingly recognized as one of the potential contributors to GDM development. A recent meta-analysis has shown that vitamin D deficiency is associated with the risk of GDM. The relation between GDM and vitamin D deficiency seems to be a two-way street, as

- Low values of vitamin D increase the risk of GDM;
- Women with GDM were more likely to develop vitamin D deficiency compared to pregnant women with normal vitamin D levels.

Unfortunately, no large randomized controlled trial on vitamin D in women at high risk for GDM has been published as yet, and it remains to be proved whether vitamin D deficiency contributes to the development of GDM.²⁵⁻²⁸

Thus, any clinical conclusions should be interpreted with caution.

GDM and Metabolically Associated Steatotic Liver Disease (MASLD)

MASLD may be a risk factor for the development of any type of DM, including T1, T2, or GDM. There is a bilateral positive association between MASLD and GDM:

- Studies reported that MASLD risk is significantly higher in women with GDM. GDM is a new risk factor for MASLD that affects the course of the disease independently throughout life.
- Still other studies reported that the GDM development risk was substantially higher in women who, independent of their BMI (normal or elevated), were diagnosed with MASLD. GDM is associated with increased postpartum risk for MASLD^{29,30}

Feto-Maternal Complications of GDM

GDM is associated with a wide range of both maternal complications during pregnancy, labor, postpartum, and beyond, and fetal congenital and neonatal complications and poor long-term outcomes.³¹

Feto-Maternal Outcomes of GDM and the Role of GDM Screening

GDM is a major pregnancy complication associated with increased morbidity and mortality for the mother, fetus, and baby. A fetal and neonatal mortality rate was as high as 65% before

the development of specialized maternal and neonatal care. GDM that stays undiagnosed and untreated results in adverse pregnancy outcomes.

Thus, the purpose of screening, treatment, and management of GDM is aimed at the prevention of poor pregnancy outcomes.

GDM screening is important, as it:

1. reduces maternal, fetal, and newborn mortality and morbidity;
2. allows the reduction of the risk of GDM in women with a history of GDM in anamnesis;
3. prevents the transmission of DM and metabolic disorders from one generation to another.

Prevention of GDM

GDM is not totally preventable, but there are ways to help lower the risk!

Environmental risk factors must be considered in the prevention of GDM. Control and elimination of environmental and socioeconomic risk factors comprise the population strategy and are the responsibility of the State and Government.¹⁸

A high-risk strategy is aimed at the elimination of risks existing in the high-risk population. Influencing reversible individual risk factors, such as obesity and waist circumference. Unhealthy diet, physical inactivity, smoking, etc., are primarily the responsibility of each individual.

According to the 2019 Research Trusted Source, the ideal time to influence individual risk factors is around pregnancy.³²

Measures to reduce the potential risks of GDM development include:

- Elimination of reversible individual risks means:
- Maintenance of healthy body weight;
- In case of overweight, losing 5-7% of body weight;
- Once pregnant, a woman should not lose weight unless it is needed;
- If a woman's condition allows, performing regular physical activity;
- During pregnancy, walking and swimming are good and safe;
- Inclusion of fiber in each meal (vegetables, greens, fruit)
- Limiting sweets (especially from beverages and desserts)
- Blood sugar testing as early as three months before conception, if a woman has a history of GDM and she is planning pregnancy;
- Planning of each subsequent pregnancy, if a woman had GDM in a prior pregnancy;
- If GDM risk factors are present, then screening tests should be performed in the first trimester to see if the condition has developed again

The best time to lower the risk of GDM and make lifestyle changes is during family planning or a long time before getting pregnant!

Treatment of GDM

If GDM is revealed during screening, treatment should be initiated immediately. Treatment of GDM includes:

- Special meal plans;
- Scheduled physical activity;
- Daily blood glucose testing (in GDM);
- Insulin injections (in GDM, if needed);
- Metformin (if needed).³³

Conclusion

Aggressive influence of risk factors, mainly reversible environmental, socio-economic, and individual ones, has led to a critical increase in GDM prevalence in high-, middle-, and low-in-

come countries. GDM that is not diagnosed, or is diagnosed late, or if proper treatment is not provided, shows high feto-maternal morbidity and mortality.

Timely and correct screening is essential for the prevention of GDM complications and fetal programming in adult life.

Though GDM cannot be totally prevented, a lot can be done to lower the risk, as what happens in the womb lasts all life!

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CHANGE OF RHEOLOGICAL STATUS AND FIBRINOGEN, AS MARKERS OF THE BLOOD CIRCULATORY SYSTEM, IN DIFFERENT PREGNANCY TRIMESTERS

MAKA MANTSKAVA, MD, PhD;¹ NANA MOMTSELIDZE, MD, PhD;²

GIORGI KUCHAVA, MD, PhD³

¹ *Ivane Beritashvili Center of Experimental Biomedicine, Department of Rheology and Diagnostic Analytical Services, Tbilisi, Georgia; President, International Society of Rheologists; National Head, World Society of Clinical Hemorheology and Microcirculation*

² *Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia; UNIK-Kutaisi University, Kutaisi, Georgia*

³ *Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia*

ABSTRACT

We studied the rheological profile and fibrinogen in healthy pregnant women in the I, II, and III trimesters, and a control group of women in the 2nd phase of the menstrual cycle. It turned out that rheological changes in different trimesters are heterogeneous and do not always correlate with the percentage changes in fibrinogen. Having discussed the data, we concluded that studying the full spectrum of rheological status is advisable to determine blood fluidity.

Keywords: aggregation; deformation; plasma viscosity; healthy pregnant; fibrinogen

Introduction

The regular operation of the circulatory system involves the interaction of the heart, arterial and venous vascular systems, blood volume, and viscosity. The pumping function of the heart depends on complex cardiomechanical processes, such as the inflow and outflow of blood to the heart. Acute circulatory failure is based on cardiac and vascular heart failure, which are the subject of study in clinical biomedicine, particularly cardiology. Clinical rheology, an integral part of this field, studies the fluidity of blood in micro and macro vessels. A change in the work of the heart entails a reaction from the microcirculation and microcirculation systems and the formation of compensatory mechanisms. The macrocirculation system includes: 1) a Cardiac pump, 2) Buffer vessels (arteries), and 3) Capacitor vessels (veins).

The microcirculation system includes 1) Resistance vessels (arterioles, venules), 2) Exchange vessels (capillaries), and 3) Shunt vessels (arteriole-venous anastomoses).

Blood flow must be adequate. This definition was introduced into world literature by Giorgi

Mchedlishvili.¹⁻³ He is the founder of clinical rheology in the world.

Characteristics of adequate blood have mathematical approaches.⁴

Heart performance is assessed by stroke volume and cardiac output.

$$SV = EDV - ESV$$

$$CO = SV \times HR$$

The cardiac output depends on the preload, determined by the venous return required for the stroke volume, and afterload, which is made up of the pressure in the aorta and the total vascular resistance.

PVR is calculated using the Poiseuille formula: $PVR = (1333 \times MDP \times 60)/MV$. Cardiac output: $MDP = \frac{PP}{3} + DP$ $CO = \frac{PP}{3} + DD$ If you have data on PVR and know the SI (cardiac index), you can determine the patient's blood circulation type. In obstetrics, where the postural syndrome acts in the same direction, a critical decrease in venous return may occur. Also, the types of blood circulation correlate with the uteroplacental blood flow (the most favorable is eukinetic).

Pregnancy places increased demands on the circulatory system, but at the same time includes mechanisms to meet them. The first of these mechanisms is an increase in the circulating blood volume. The average increase in water during pregnancy is from 6 to 8 liters, of which 4-6 liters are in the extracellular sector.

Most critical conditions that determine not only maternal but also perinatal mortality are accompanied by severe disturbances in water balance. There are three types of capillaries. In the arterial part, hydrostatic pressure predominates; in the middle, it is balanced with colloid-osmotic pressure; and in the venous part, colloid-osmotic pressure predominates. If blood pressure decreases or (and) colloid-osmotic pressure increases, then filtration decreases and reabsorption increases. The body compensates for the deficit of circulating blood volume (from the interstitium).⁵

If systemic blood pressure increases and colloid-osmotic pressure decreases, then filtration increases and reabsorption decreases, i.e., "the capillary drains excess fluid into the interstitial space.

Pregnancy brings about profound changes in the woman's cardiovascular system to meet the increased oxygen and nutrient needs of the mother and developing fetus.⁶

From the very beginning of pregnancy, the woman's blood flow begins to increase, peaking by the third trimester. This increase in blood flow provides enough oxygen and nutrients to support the growing fetus and the changing mother.

The heart begins to pump more blood with each beat, increasing cardiac output. This change helps provide the fetus with the resources it needs to thrive.

Vasculines dilate, which reduces total peripheral resistance and allows blood to flow freely to essential organs, including the placenta.

The mother's body adapts to cope with the increased demands on the cardiovascular system. The volume of circulating blood increases, which supports circulatory efficiency and the delivery of oxygen and nutrients.

The changes in blood flow and the vascular system during pregnancy are important adaptations that help support the viability and development of the fetus. Adequacy of blood circulation occurs at the level of rheological status of blood, which is provided by red blood cells, especially erythrocytes. Therefore, our study aimed to investigate the rheological status in pregnant women in different trimesters.

Materials and Methods

We investigate pregnant women (24-32years old). We investigate them in 4-13 weeks of gestation (first point of study), and next in 13-26 gestation weeks (second point of study), and next 37-38 gestation weeks (third point of study). The control group consisted of 14 practically healthy women in the 2nd phase of the menstrual cycle. The Ethics Committee of the Society of Rheology approved the research design.

Inclusion parameters: First pregnancy.

Exception parameter: Hematological diseases in history, cancer, and anemia of pregnant women.

For a detailed description of the rheological status of blood, we studied erythrocyte aggregation, erythrocyte deformability, plasma viscosity, rheological index of red blood, and fibrinogen in pregnant women in the first, second, and third trimesters and compared them with control values.

The index of red blood cell aggregability (EAI)

The index of red blood cell aggregability represents the aggregated red blood cells' area ratio against the whole area of the red blood cells. Red blood cell aggregation was evaluated using the recently developed "Georgian technique", which provided us with direct and quantitative data. Blood samples (4ml) from the cubital veins were centrifuged, and about 0.1 ml of blood was diluted 1:200 in its own plasma in the Thoma pipettes, and then preliminary rinsed with 5% sodium citrate solution without the addition of any other anticoagulants to the blood under study. The diluted blood was placed into a glass chamber 0.1 mm high after standard mixing. The quantitative index of red blood cell aggregation, which was assessed with a special program at the Texture Analysis System (TAS-plus, Leitz, Germany), represented the relationship between the aggregated and unaggregated red cells.⁷⁻⁹

Red blood cell deformability index (EDI)

Evaluation of red blood cell deformability was performed with the aid of the nucleopore membrane filter method, which is based on assessing the velocity of the red blood cells' passage through the tiny pores (5 μm , which is a diameter of the smallest capillary) of the filter, at constant pressure (10 cm of water column) and temperature (37°C). Obtaining the pure red blood cells was performed by centrifuging the blood sample at 3000 rpm for 15 min. The resulting plasma was aspirated with a micropipette, and the remaining blood cells were added with bovine serum albumin (0.2 mg per 5 ml) dissolved in a phosphate buffer. Then, the blood was centrifuged a second time at 1000 rpm for 5 min. The precipitated red blood cells and a thin layer of leukocytes and thrombocytes were separated from the phosphate buffer. This procedure was repeated three times. Purified red blood cell mass was diluted in the phosphate buffer with a hematocrit of 10%. The evaluation of the deformability index involved measuring the velocity of red blood cell passage through the filter (mm/min). The high-quality polycarbonate filters (with 5 μm diameter pores) were used in measuring procedures.⁷⁻⁹

Plasma viscosity

Blood plasma viscosity was examined in a capillary viscometer at 37 °C. The Diameter of the capillary was about 1.8 mm. The displacement of plasma samples was induced by the gravitational force related to the difference in the levels of the plasma under study, about 65. (without ap-

plication of additional pressure) For the evaluation of the plasma viscosity in centipoises (cP), we determined the calibration factor (F). Blood plasma viscosity was calculated by multiplying the time for plasma displacement through the capillary by the instrument calibration factor.⁷⁻⁹

Blood rheological index in silico (BRI)

We used a new rheologically significant parameter - the Blood Rheological Coefficient (BRI) to study blood rheology. The BRI is a complex indicator that mathematically reflects such indicators as the number of erythrocytes, their overall size, volume, and the amount of hemoglobin in each of them. The calculation of the BRI gives the clinician a comprehensive view of all the independent parameters of the red blood cells involved in the formation of laminar or turbulent flow, depending on blood viscosity.

Thus, if we assume that the viscosity of the plasma is constant, then the BRI is responsible for haematology.

If we analyze each of the parameters we are investigating from the point of view of its physical significance, we get that.

$$RDW = \frac{\max(OS)}{\min(OS)} \quad (1)$$

The parameter of red blood cell distribution is the ratio of the largest red blood cell to the smallest red blood cell. It follows from (1) that

$$\max(OS) = RDW \times \min(OS) \quad (2)$$

On the other hand, if we multiply the total number of red blood cells by the average haemoglobin, we get the numerical value of haemoglobin

$$\max(OS) + \min(OS) = RBC \times MCH \quad (3)$$

It follows from (3) that

$$\max(OS) = RBC \times MCH - \min(OS) \quad (4)$$

On the other hand, the volume of a red blood cell is equal to the sum of all red blood cells with large dimensions and all red blood cells with smaller dimensions divided by "2", if n is the number of red blood cells with large dimensions, and (RBC - n) is the number of red blood cells with smaller dimensions

$$MCV = \frac{((\max(OS) \times n) + (\min(OS) \times (RBC - n)))}{2} \quad (5)$$

Hence, it follows that

$$\max(OS) \times n + \min(OS) \times (RBC - n) = 2MCV \quad (6)$$

Thus, if we group formulas (2), (4), and (6) into a system of equations, we have three unknowns and three easily solvable equations in the system

$$\begin{cases} \max(OS) = RDW \times \min(OS) \\ \max(OS) = RBC \times MCH - \min(OS) \\ \max(OS) \times n + \times (RBC - n) = 2MCV \end{cases}$$

where $\max(OS) \times n$ is the coefficient of red blood cells Fibrinogen.

We study the determination of fibrinogen using the Rutberg method. The analysis is a gravimetric method; that is, to determine the fibrinogen level, the weight of the formed clot is measured. The method of studying fibrinogen, according to Rutberg, is as follows. First, it is necessary to obtain a fibrin clot. Thromboplastin (the third factor of the coagulation system) with calcium is added to the obtained biological material (blood plasma). Then, the resulting clot is dried, removing the remaining plasma with filter paper, and washed. Only then is the mass of the precipitated fibrin estimated, and the fibrinogen content is determined from it.

Statistical analysis.

Statistical significance was tested using one-way ANOVA and a two-sample test. Relationships yielding P-values less than 0,05 were considered significant. All values were expressed as the mean $\pm$ standard error.

Results

Our studies showed that all rheological parameters and fibrinogen changed in the first trimester compared to the norm, as well as in comparison with the second and third trimesters of the same patients. Heterogeneous changes were observed between the second and third trimesters. You can see the details in Table 1.

Discussion

Changes in blood rheology in the first trimester of pregnancy are associated with complex hormonal, vascular, and metabolic changes to ensure normal fetal development and adaptation of the mother's body. Increased levels of estrogens and progesterone lead to changes in vascular tone and increased vascular permeability. Active production of human chorionic gonadotropin stimulates changes in the hemostasis system. In the first trimester, an increase in plasma volume begins, leading to hemodilution and a decrease in hematocrit, which leads to changes in rheological status. Our studies confirmed this. There is an increase in the level of fibrinogen, coagulation factors, and aggregation capacity of platelets, which subsequently affects the change in the rheology of red blood, as shown by our studies. Due to the increase in plasma volume, the blood becomes less viscous, which improves its fluidity and microcirculation. This is important for the normal functioning of the placenta and the blood supply to the fetus. Their deformability increases to improve permeability through capillaries. This is one of the adaptation moments.¹⁰

In the second trimester of pregnancy, changes in blood rheology continue and intensify, adapting the mother's body to the growing needs of the fetus. The main mechanisms of these changes are associated with increased blood volume, changes in plasma composition, and strengthening of the hemostasis system. By mid-pregnancy, plasma volume increases by 30-40%, and the number of red blood cells by only 20%. This leads to physiological hemodilution (blood thinning) and a relative decrease in hematocrit. Due to hemodilution, blood viscosity decreases, which improves microcirculation and blood supply to the placenta. However, the balance between fluid and formed elements must be maintained to avoid blood stagnation

and hypoxia; the fibrinogen level increases. The activity of fibrinolysis decreases, which makes the blood more prone to thrombosis. This is an important mechanism for protecting against blood loss in case of possible complications of pregnancy and childbirth. Increased platelet activation compensates for blood thinning and helps maintain optimal hemostasis. An environment that increases platelet aggregation becomes favorable for increased red blood cell aggregation. This is confirmed by an increase in the rheology coefficient in our studies. High estrogen levels promote vasodilation, improving blood flow. Progesterone maintains vascular tone, preventing excessive blood viscosity. In response to increased oxygen demand, erythropoietin levels increase, stimulating the formation of new red blood cells. Our studies confirm this.¹¹

In the third trimester of pregnancy, blood rheology continues to change. The main changes include increased hypercoagulability, further increase in circulating blood volume, and adaptation of the vascular system. By the end of pregnancy, the circulating blood volume increases by 40-50% compared to the control. This ensures placental blood flow. Due to the imbalance between plasma and erythrocytes, physiological anemia of pregnancy persists. Fibrinogen levels increase sharply. Functional activity and the tendency to aggregation increase.^{12,13} Our studies confirm this.

The parallelism of rheological status and blood circulation is a reliable physiological effect. Naturally, this also occurs during physiological pregnancy. For this purpose, the study of rheological status in pregnant women is one of the informative analyses.

Table 1. Parameters of rheological status and fibrinogen in the control group women and healthy pregnant women in different trimesters (M ± m)

Parameter	Unit	Control (N = 20)	I trimester (N = 20)	II trimester (N = 25)	III trimester (N = 25)
EAI	%	24 ± 2.3	31 ± 4.5*	26 ± 2.9	33 ± 4.5*
EDI	%	2.1 ± 0.01	2.2 ± 0.03	2.1 ± 0.04	2.2 ± 0.01
PV	sP	1.13 ± 0.05	1.15 ± 0.05	1.14 ± 0.05	1.13 ± 0.05
RI	unit	1.00 ± 0.05	1.15 ± 0.05*	1.10 ± 0.05	1.10 ± 0.05
Fibrinogen	g/L	2.6 ± 0.5	3.5 ± 0.7*	4.6 ± 0.9*	5.2 ± 0.6*

Abbreviations (by order of use in the text)

SV - stroke volume

CO - cardiac output

HR - heart rate

MDP - mean dynamic pressure

EDV - end diastolic volume

ESV - end systolic volume

TVR - total vascular resistance

PVR -peripheral vessels resistance

PP - pulse pressure

DP - diastolic pressure

PV - plasma viscosity

IR - index resistance
EAI - erythrocytes aggregation index
EDI - erythrocytes deformation index
BRI - blood rheological coefficient
MCH - mean corpuscular volume
MCV - mean corpuscular hemoglobin
RDW - red cell distribution width
OS - overall size of red cell distribution width
MCH - mean corpuscular hemoglobin

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COMPARATIVE ANALYSIS OF VAGINAL AND RECTAL PROGESTOGEN ADMINISTRATION IN PREGNANT WOMEN WITH THREATENED MISCARRIAGE BEFORE 21 WEEKS OF GESTATION

AHMAD KARIMOV, Prof.;¹ **MAVLYUDA ALIYEVA**, Master's Student²

¹ Department of Obstetrics and Gynecology, Family Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan

² Department of Obstetrics and Gynecology, Family Medicine, Tashkent Medical Academy, Tashkent, Uzbekistan

ABSTRACT

Threatened miscarriage represents one of the most frequently encountered complications of early pregnancy, characterized predominantly by vaginal bleeding, cramps, and occasional cervical change without the expulsion of fetal tissue. Despite advances in obstetric management, the optimal therapeutic approach remains a subject of ongoing debate, particularly concerning the route of progesterone administration. Vaginal and rectal progesterone formulations are frequently used to support early gestation, yet comparative evidence on their relative efficacy remains limited. This prospective randomized controlled study aimed to evaluate and compare the effectiveness of vaginal versus rectal micronized progesterone administration in women with threatened miscarriage, focusing on pregnancy continuation, symptom resolution, and patient satisfaction. The study further sought to explore patient acceptability, tolerability, and the impact of treatment route on anxiety levels associated with early pregnancy complications. By adopting a multicenter design and incorporating patient-centered outcomes, the trial introduces valuable insight into both clinical and psychosocial dimensions of threatened miscarriage care. Findings demonstrated that vaginal administration resulted in higher pregnancy continuation rates (90.0% vs. 76.7%), faster symptom resolution, and markedly greater patient satisfaction compared with rectal administration. Moreover, the use of vaginal progesterone was associated with improved adherence and reduced discontinuation rates, emphasizing the importance of delivery comfort in early pregnancy therapeutics. The results suggest that tailoring treatment not only to physiological effectiveness but also to personal preference may enhance outcomes in women experiencing threatened miscarriage. These findings underscore the clinical utility of vaginal progesterone in the management of threatened miscarriage and support its preferential use in routine obstetric practice.

Keywords: threatened miscarriage; vaginal bleeding; progesterone therapy; pregnancy continuation; vaginal route; rectal administration; randomized trial; micronized progesterone; early pregnancy bleeding; cervical stability; maternal-fetal interface; uterine receptivity; cytokines; immune modulation; patient compliance; tolerability; treatment satisfaction

Introduction

Threatened miscarriage remains a commonly encountered complication of early gestation and affects approximately 15-20 % of clinically recognized pregnancies worldwide.^{1,2} It is clinically defined as vaginal bleeding, with or without cramping pain, in the presence of a closed cervical os and a viable fetus. Recent years have seen a rising trend in the number of women presenting with first-trimester bleeding, possibly due to increased awareness and accessibility of early ultrasonography. While many pregnancies continue uneventfully following conservative management, others unfortunately culminate in spontaneous pregnancy loss, which has profound emotional and psychological effects on affected couples. Managing threatened miscarriage effectively has therefore become an essential goal in reproductive medicine to enhance pregnancy survival and reduce anxiety. Progesterone is a steroid hormone produced primarily by the corpus luteum in early pregnancy and the placenta later in gestation. It plays a critical biological role in maintaining uterine quiescence, suppressing myometrial contractility, and promoting immune tolerance at the maternal-fetal interface.^{3,4} Progesterone deficiency has long been implicated in early pregnancy failure, providing the rationale for the therapeutic use of exogenous progestogens in threatened miscarriage.⁵ Over time, different routes of progesterone administration have been investigated, including oral, intramuscular, subcutaneous, rectal, and vaginal formulations. However, due to the poor bioavailability and extensive first-pass effect associated with oral administration, vaginal and rectal routes are generally preferred in clinical practice.⁶ Vaginal progesterone is favored due to the so-called uterine first-pass effect, which delivers high concentrations directly to the endometrium. In contrast, rectal progesterone is often reserved as an alternative in cases where the vaginal route is not acceptable or contraindicated.

Despite multiple studies supporting the use of progesterone in threatened miscarriage, considerable variation exists regarding the optimal dose, duration, and route of delivery across different obstetric centers. Previous clinical trials and meta-analyses have suggested a reduction in miscarriage rates with progesterone supplementation. Yet, direct comparative studies between vaginal and rectal routes remain limited in number and sample size.^{7,8} In addition, many published studies have focused primarily on biochemical outcomes, with few examining patient-centered measures such as comfort, satisfaction, and ease of administration. These aspects are increasingly recognized as crucial in determining adherence and overall treatment success.

Given these considerations, further high-quality research is required to inform evidence-based management strategies for threatened miscarriage. The present prospective randomized controlled trial was therefore designed to address this gap by comparing the efficacy, safety, and acceptance of vaginal versus rectal micronized progesterone in women presenting with threatened miscarriage prior to 21 weeks' gestation. By evaluating not only pregnancy continuation but also symptom resolution and patient satisfaction, this study aims to provide a more comprehensive understanding of the clinical utility of both treatment routes in real-world obstetric practice. Furthermore, threatened miscarriage has been increasingly described as a

multifactorial condition involving not only hormonal insufficiency but also impaired placentation, oxidative stress, and dysregulated inflammatory responses. Emerging evidence suggests that alterations in cytokine profiles, such as increased levels of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), may destabilize the maternal-fetal immune balance, promoting uterine contractility and cervical ripening. Progesterone has been shown to counteract these pro-inflammatory pathways, reducing local inflammatory signaling through progesterone-induced blocking factor (PIBF), and thereby enhancing maternal immune tolerance. Several recent studies have also investigated the role of micronized progesterone in improving uterine artery blood flow indices in women with suboptimal placentation during early pregnancy, adding vascular support as a further potential mechanism of benefit. Given this expanding understanding of progesterone's pleiotropic roles, the route of administration becomes highly relevant; delivering the hormone closer to the target tissues in the uterus may ensure more optimal modulation of local endocrine-immune crosstalk. In this context, the current study not only aims to address the classical parameters of clinical efficacy but also to establish a practical framework for delivering progesterone in a way that supports both biological plausibility and patient acceptability in routine obstetric care.

Aim of the Work

To improve the clinical management strategies for pregnant women diagnosed with threatened miscarriage by comparing the therapeutic outcomes of vaginal versus rectal progesterone administration in terms of pregnancy continuation, symptom resolution, adverse effects, and patient satisfaction.

Study Design and Setting

A prospective, multicenter, randomized controlled clinical trial was conducted at the Department of Obstetrics and Gynecology, Tashkent Medical Academy, Uzbekistan, from December 20, 2023, to November 27, 2024. The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB Reference No. 054/2023-OBGYN). Written informed consent was obtained from all participants prior to inclusion.

Participants

A total of 60 pregnant women with sonographically confirmed intrauterine pregnancy between 6 and 21 weeks of gestation were enrolled. Participants were recruited from outpatient clinics and emergency obstetric departments. Detailed medical histories were obtained, and experienced obstetricians performed physical examinations.

Inclusion criteria:

- Age between 18 and 40 years
- Confirmed viable intrauterine pregnancy
- Clinical diagnosis of threatened miscarriage (vaginal bleeding $\pm$ lower abdominal pain, closed cervix)
- Ability and willingness to comply with the study protocol and give consent

Exclusion criteria:

- History or ultrasonographic evidence of missed miscarriage, spontaneous abortion, molar pregnancy, or ectopic pregnancy

- Multiple pregnancy or significant fetal anomalies
- Uterine malformations or cervical insufficiency
- Previous preterm labor or cerclage
- Contraindications to progesterone therapy (e.g., active liver disease, breast carcinoma, thromboembolic disorders)
- Inability to tolerate vaginal or rectal administration

Randomization and Group Allocation

Eligible participants were block-randomized in a 1:1 ratio using a computer-generated sequence and concealed envelopes into one of two treatment groups:

- Group A: Vaginal micronized progesterone 200 mg nightly
- Group B: Rectal micronized progesterone 200 mg nightly

Randomization was stratified based on the presence or absence of vaginal bleeding at enrollment to ensure balanced distribution.

Intervention

Both groups received micronized progesterone (manufactured by X Pharmaceutical Company), administered as suppositories. Treatment was initiated immediately following diagnosis and continued for 14 days. Participants were advised to follow standard obstetric precautions (pelvic rest, avoidance of strenuous physical activity). Compliance was assessed at follow-up visits and via treatment diaries.

Outcomes

Primary outcome:

- Continuation of pregnancy beyond 24 weeks of gestation

Secondary outcomes:

- Time to cessation of vaginal bleeding
- Time to relief of abdominal cramping
- Rate of symptom resolution (≤ 3 days; ≤ 7 days; > 7 days)
- Incidence and severity of adverse effects (local irritation, gastrointestinal complaints, headache, dizziness)
- Patient-reported satisfaction (ease of use, comfort, overall satisfaction – assessed by Likert scale 1-5)

Data Collection

Data were collected at baseline, day 7, day 14, and at 24-week follow-up. Baseline variables included maternal age, parity, body mass index (BMI), gestational age, obstetric history, and presence of vaginal bleeding. During follow-up, symptom progression, adverse events, and patient preference were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as mean $\pm$ standard deviation (SD) or percentages. Chi-square and Fisher's exact tests compared categorical variables; an independent samples t-test was used for continuous variables. Multivariate logistic regression was conducted to adjust for

confounders, including age, gestational age, and parity. A p-value < 0.05 was considered statistically significant.

Results

A total of 60 participants were recruited and completed the study, with 30 women in each treatment arm. Baseline demographic and clinical characteristics were comparable between the vaginal and rectal progesterone groups, indicating successful randomization (Table 1).

Table 1. Demographic characteristics of participants (n=60)

Variable	Vaginal Group (n=30)	Rectal Group (n=30)	Total
Age (years)	28.5 ± 4.1	29.2 ± 4.4	28.8 ± 4.3
Gestational Age (weeks)	9.0 ± 2.3	9.2 ± 2.1	9.1 ± 2.2
Primigravida	18 (60%)	16 (53%)	34 (56.7%)
Multigravida	12 (40%)	14 (47%)	26 (43.3%)
BMI (kg/m ²)	24.9 ± 3.6	24.5 ± 3.5	24.7 ± 3.5
Previous Miscarriage	11 (36.7%)	10 (33.3%)	21 (35%)

Primary Outcome

Pregnancy continuation beyond 24 weeks was significantly higher in the vaginal progesterone group compared to the rectal group (90% vs. 76.7%, p = 0.05) (Table 2), suggesting superior efficacy of the vaginal route.

Secondary Outcomes

While symptom resolution within 7 days occurred more frequently in the vaginal group (88.6%) versus the rectal group (74.3%), this difference was not statistically significant (p=0.07). Early symptom relief (≤3 days) was also more common with vaginal progesterone (63.3% vs. 50%; p=0.15).

Overall patient satisfaction (Likert scale) was significantly greater in the vaginal group (4.3 ± 0.6 vs. 3.8 ± 0.7; p=0.03), with better scores for ease of use and comfort. Treatment preference strongly favored the vaginal route (66.7% vs. 33.3%; p=0.01).

Table 2. Demographic characteristics of participants (n=60)

Outcome	Vaginal Progesterone	Rectal Progesterone	p-value
Pregnancy continuation (%)	90.0%	76.7%	0.05
Symptom resolution ≤7 days	88.6%	74.3%	0.07
Early resolution ≤3 days	63.3%	50.0%	0.15
Patient satisfaction (mean)	4.3 ± 0.6	3.8 ± 0.7	0.03
Adverse effects (any)	16.7%	20%	0.58

Adverse Events

Adverse effects were generally mild (Table 3), with no significant differences between groups. Vaginal irritation was more common in the vaginal group (13.3%), whereas gastrointestinal discomfort prevailed in the rectal group (13.3%). No serious adverse events were observed.

Table 3. Adverse effects profile

Adverse effect	Vaginal (n=30)	Rectal (n=30)	p
Vaginal irritation	4 (13.3%)	2 (6.7%)	0.44
GI discomfort	2 (6.7%)	4 (13.3%)	0.29
Headache	3 (10%)	2 (6.7%)	0.59
Dizziness	2 (6.7%)	3 (10%)	0.65
No adverse effects	25 (83.3%)	24 (80%)	0.75

Follow-up Outcomes at 24 Weeks

Live birth rate was higher in the vaginal group (86.7%) compared to the rectal group (76.7%), although this did not reach statistical significance ($p=0.22$). The miscarriage rate was lower in the vaginal group (10%) versus the rectal group (16.7%), and no differences were seen for preterm birth or neonatal complications (Table 4).

Table 4. Adverse effects profile

Outcome	Vaginal group	Rectal group	p
Live birth (%)	86.7%	76.7%	0.22
Miscarriage (%)	10.0%	16.7%	0.31
Preterm birth (%)	3.3%	3.3%	1.00
Neonatal complications (%)	6.7%	3.3%	0.60

Discussion

The findings from this randomized clinical trial clearly indicate that vaginal micronized progesterone is more effective than rectal progesterone in improving pregnancy continuation and patient satisfaction among women experiencing threatened miscarriage. This supports the biological advantage of vaginal progesterone, which delivers high concentrations directly to the uterus through the local first-pass pathway, resulting in more substantial endometrial exposure and more pronounced inhibition of uterine contractility. By contrast, rectal absorption is slower and depends on inter-individual differences in gastrointestinal perfusion, which may account for lower therapeutic efficacy. Our results resonate with previous observational and interventional studies that demonstrated superior obstetric outcomes in women receiving intravaginal progesterone supplementation [9,10]. In the context of threatened miscarriage, even moderate improvements in symptom resolution times – such as faster cessation of bleeding and relief of cramping – can have meaningful psychological benefits, reducing patients' anxiety and improving adherence to pregnancy-preserving advice. The trend toward

earlier symptom relief observed in the vaginal group is therefore clinically relevant, even when not always statistically significant in smaller trials.

Another significant contribution of this study is the inclusion of patient-reported satisfaction, which is often overlooked in reproductive medicine despite being essential for compliance. Women receiving vaginal progesterone reported significantly greater ease of use, comfort during administration, and overall satisfaction compared to those receiving rectal suppositories. These outcomes align with qualitative reports suggesting that rectal medications are perceived as inconvenient and culturally less acceptable in many populations. Hence, beyond physiologic effectiveness, the vaginal route may offer a practical advantage by increasing patient willingness to continue therapy throughout the vulnerable first trimester. Nevertheless, the rectal route still has a vital role in selected clinical situations. Women suffering from vaginal infections, active bleeding that prevents absorption, or those with specific cultural or religious reservations regarding intravaginal application may benefit from rectal progesterone as a viable alternative. Furthermore, advancements in rectal suppository formulation could potentially improve future absorption profiles and acceptability. The present study is subject to certain limitations that should be considered when interpreting the results. The sample size of 60 participants, although sufficient to detect differences in the primary outcome, limits the power to evaluate rarer adverse events or obstetric complications such as preterm birth. Another limitation is the follow-up period to only 24 weeks of gestation; extending evaluation through delivery and neonatal outcomes would offer a more complete picture of long-term safety and effectiveness. Despite these limitations, the randomized design, multicenter involvement, and inclusion of both clinical and patient-centered endpoints enhance the validity and relevance of our findings. In light of current results, clinicians should consider vaginal progesterone as the first-line option for managing threatened miscarriage whenever feasible. Future large-scale multicenter trials are strongly recommended to assess whether adjunctive strategies – such as combining progesterone with other agents (e.g., human chorionic gonadotropin or immunomodulators) – could further improve pregnancy continuation in high-risk women. In addition, ongoing research into personalized medicine approaches, including identification of biomarkers predicting progesterone responsiveness, may help optimize treatment strategies in early pregnancy care. The psychosocial dimension of threatened miscarriage management is increasingly recognized as a critical aspect of overall care, and the choice of progesterone route may influence a woman's perceived control and emotional well-being during a vulnerable period. Women who experience rapid relief of bleeding symptoms have been found to report significantly lower anxiety scores, contributing to better overall psychological outcomes in early pregnancy. The improved satisfaction associated with vaginal progesterone in our trial may therefore confer not only physiologic benefits but also indirect advantages via reduction of stress-related neuroendocrine responses that could themselves adversely affect pregnancy continuation. Additionally, recent pharmacokinetic data indicate that vaginal administration results in higher endometrial tissue concentrations of progesterone with lower systemic peaks, thus minimizing side effects such as dizziness or drowsiness that often reduce compliance with rectal or oral regimens. Given the multifaceted role of progesterone and the sensitive emotional context of threatened miscarriage, selecting the route that ensures both efficacy and psychological comfort is vital for maximizing outcomes. Future research should also explore the impact of combining vaginal progesterone with psychosocial support interventions, nutritional optimization, and lifestyle counseling to provide a

comprehensive and patient-centered approach to early pregnancy preservation. Such holistic strategies may become particularly important as maternal age, assisted reproductive technology use, and environmental stressors continue to rise globally, potentially increasing the prevalence of threatened miscarriage in years to come.

Conclusion

This study demonstrates that vaginal progesterone is clinically superior to rectal progesterone for women experiencing threatened miscarriage, providing higher rates of pregnancy continuation, faster symptom resolution, and significantly better patient satisfaction. Where feasible, obstetricians should adopt the vaginal route as first-line therapy for threatened miscarriage. Rectal treatment may be reserved as a secondary alternative when vaginal administration is not tolerated. Larger studies with extended follow-up are encouraged to refine evidence-based management strategies further.

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FEMALE ORGASMIC DYSFUNCTION AND GYNECOLOGICAL PATHOLOGIES

LEVAN KOBALADZE, MD;¹ SOFIA ANDGULADZE, MD²

¹ Center for Reproductive Medicine "Universe", Tbilisi, Georgia

² Medical Corporation Evex, Tbilisi, Georgia

ABSTRACT

Background: Despite available data on the influence of gynecological pathologies on sexual dysfunction, there is no clear scientific evidence on the influence of sexual disorders, such as anorgasm, on the development of gynecological pathologies.

Objective: The objective of the study was to examine the relationship. The Objective of the study was the detection of the relationship between women's sexual functions (orgasm and libido) and gynecological pathologies.

Methods: Six hundred seventy-six sexually active women (aged 18-55 years; mean age, 31.7 ± 3 years) were investigated.. They were divided into three groups: I gr. – 148 women OVVC, II gr. – 125 women with DMV and III gr. – 403 women with other gynecological pathologies. In all groups, the frequency of orgasms and the level of libido were assessed through interviews.

Results: In I group rate of women with anorgasm (70,9%) and rare orgasms (20,9%) was significantly higher ($P<0.01$) than rate women, who had orgasms often (6,1%) or always (2,0%). In II group rate of women with anorgasm (39,2%) and rare orgasms (44,0%) was significantly higher ($P<0.01$) than women, who had orgasms often (12,8%) or always (4,0%). In III group generally was observed prevalence of women without absolute absence or presence of orgasms. As of relationship between intensity of sexual drive (libido) and frequency of orgasms – in all groups there was direct dependence - women with anorgasm and rare frequency of orgasms mainly had low or medium libido and in women, who had orgasms often or always libido was mainly medium or high.

Conclusions: Orgasmic dysfunctions (anorgasm) can promote a congestive process in the pelvis, development of varicosis of ovarian and pelvic veins (with corresponding other gynecological complications), which themselves can determine chronic pelvic pain that deepens the anorgasmic process.

In younger ages and early stages of the beginning of sexual life, timely management of anorgasmy might be a good prevention for further development of gynecological pathologies.

The issue needs further investigation to reveal the cause-and-effect relationship.

Keywords: anorgasmy; ovarico-varicocele; dilatation of myometrium veins; gynecological pathologies

Introuction

Good sexual and reproductive health is a state of complete physical, mental, and social well-being in all matters relating to the reproductive system.¹

Orgasmic dysfunction in women is one of the most important sexual disorders that determines a decrease in the quality of life in women as well as couples.

Frequency of female anorgasmy according to country data is very different:²⁻⁵ USA – 26%, Australia – 29%, Turkey – 43%, Iran – 37%, Nigeria – 55%, Brazil – 21%, China – 31%.

Dr. Elisabeth A. Lloyd summarized 32 studies conducted over 70+ years, on the frequency of women's orgasms with intercourse – intercourse alone, not orgasm with additional direct clitoral stimulation-anorgasmy-5-10%.⁶

There is a vast database on causes of sexual dysfunctions in women, indicating the most frequent factors such as anatomic, hormonal, vascular, neurological, psycho-emotional, situational, relationship problems, chronic diseases, pharmaceuticals, aging, etc.

Well investigated is also the role of gynecological pathologies and pain related to them in the development of sexual disorders.

According to Fugl-Meyer KS & Fugl-Meyer AR,⁷ a lot of women, who report manifested sexual genital pain, also report: low level of sexual interest (67%), insufficient vaginal lubrication (61%), manifested orgasmic dysfunction (48%), vaginismus (9%).

Several studies indicate the direct influence of endometriosis on the development of sexual dysfunctions in women.⁸⁻¹⁰ Stenyaeva N and co-authors in their study of women with endometriosis revealed that in the structure of sexual dysfunctions, deep dyspareunia (87.1%), decreased libido (83.3%), and coital anorgasmia (80.6%) prevailed, accompanied by disruption in sexual adaptation in the pair (93.5%). All patients demonstrated depression and anxiety. Based on literature data, it's possible to conclude that endometriosis leads to a significant disruption of the sexual health of women and marital relations and correspondingly reduced quality of life for both partners.⁸⁻¹⁰

Despite access to data on the influence of gynecological pathologies on the development of sexual dysfunctions, we couldn't find scientifically proven evidence on the influence of sexual disorders, such as anorgasmy, on the development of gynecological pathologies. Only in a few articles, dedicated to varicose extension of pelvic veins (VEPV), dyspareunia, and anorgasmy, are these conditions indicated as risk factors for the development of VEPV.^{11,12}

For us, the logical chain was under question mark: in the sexual response cycle, during the excitement and plateau phases, the blood supply of pelvic organs increases, and orgasm is the retraction mechanism for shedding blood back from these organs during the resolution phase. In cases of anorgasmic coitus, blood accumulates in the pelvic organs for an extended period, leading to venous stasis and, consequently, pelvic congestion syndrome. This condition can contribute to the development of an ovarian varicocele and the dilatation of the myometrial veins (Figures 1 and 2).

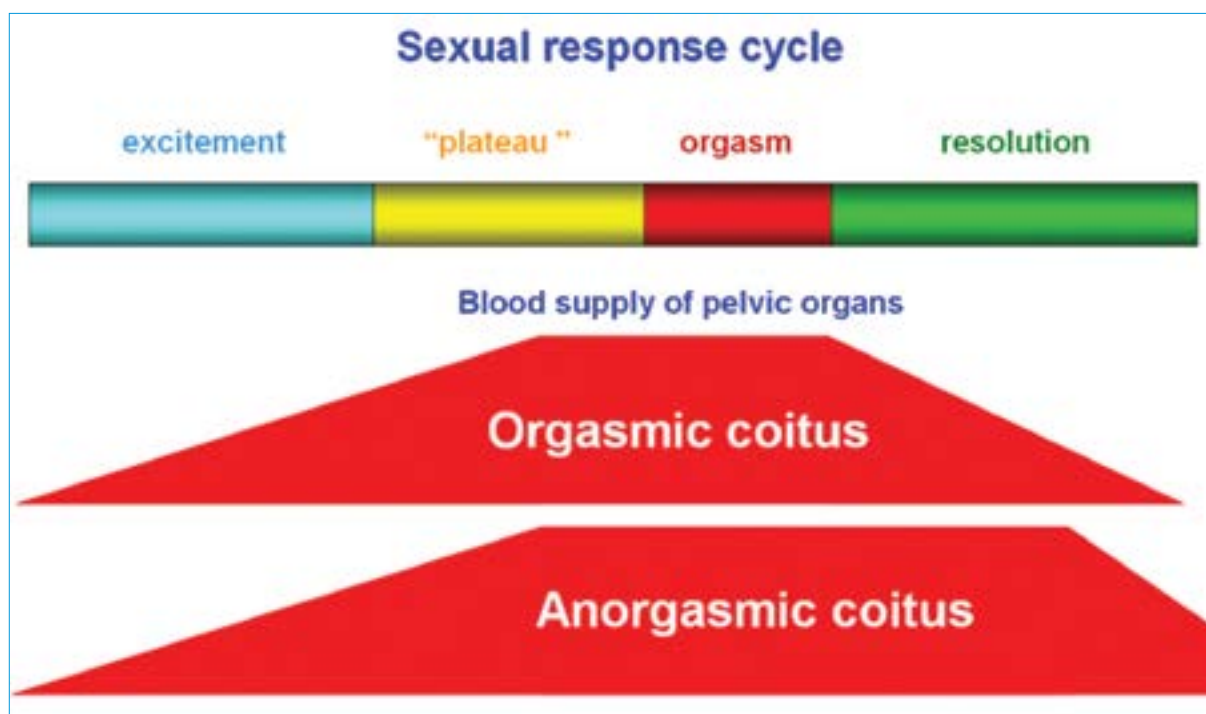


Figure 1. Blood supply of pelvic organs during anorgasmia in women.

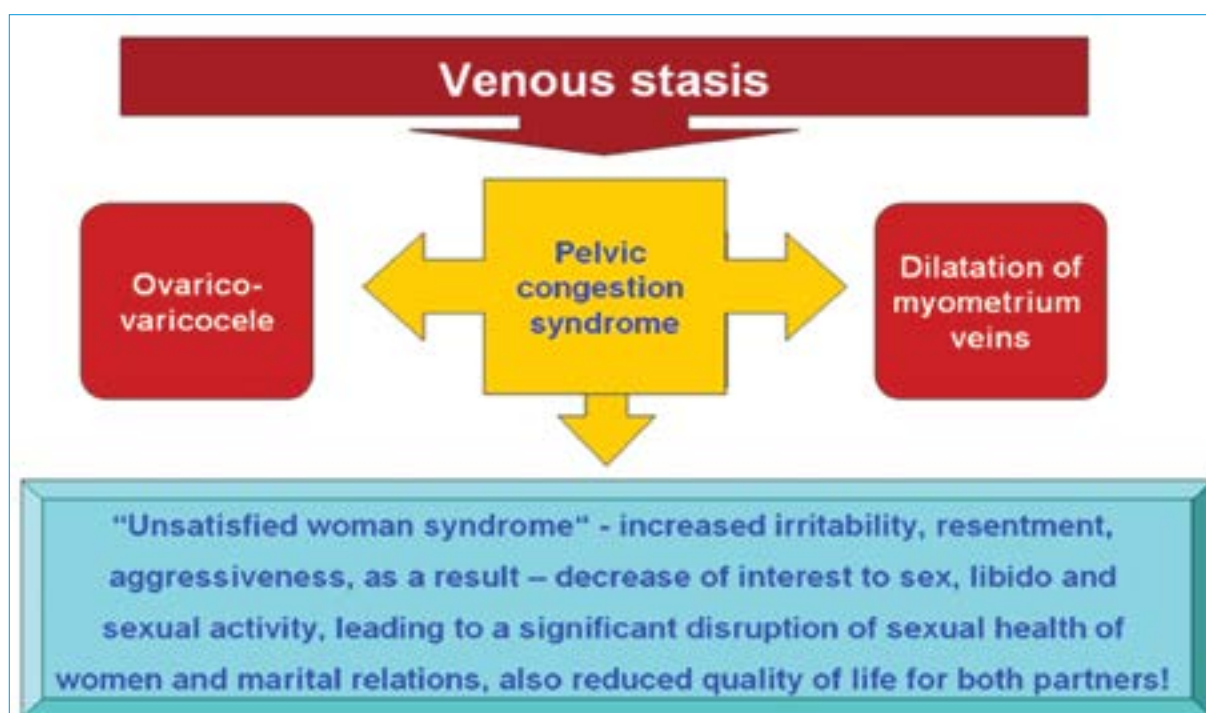


Figure 2. Anorgasmia in women – possible results.

Based on those mentioned above, the objective of our study was the detection of the **relationship between women's sexual functions (orgasm and libido) and gynecological pathologies.**

Materials and Methods

Six hundred seventy-six sexually active women (aged 18- 55 years, mean age 31,7+3) have been investigated based on the Center for Reproductive Medicine "Universe" and the out-patient clinics of Medical Corporation Evex. They were divided into three groups: I gr. – 148 women with ovarico-varicocele (OVVC), II gr. – 125 women with dilatation of the myometrium

veins (DMV) and III grade. – 403 women with other gynecological pathologies (myoma, inflammatory diseases, gynecological-endocrine disorders, etc.).

The diagnosis of patients was based on the analysis of patient records. Diagnosis of OVVC and DMV was based on the results of an investigation by transvaginal US of the pelvic venous system with Doppler examination of blood flow in the uterine veins.

In all groups, the frequency of orgasms (never, rare, often, always) and the grade of libido (low, medium, high) have been assessed by interviewing.

Statistical analysis was conducted by SPSS.21. The independent t-test was used for variables, e.g. age, duration of sexually active years and frequency of intercourse per month. Pearson's Chi-square test was performed to compare categorical data. Conclusions of the study results were based on statistically reliable results in a 95% confidence interval ($P < 0.05$).

Results

There were no statistically significant differences ($P > 0.05$) in women with different frequencies of orgasms in age, sexually active years, and number of intercourses per month.

Table 1. DAssociation of age, sexually active years, and number of intercourses per month with frequency of orgasms (Total number of investigated women: 676).

Orgasm	Number of women		Mean age	Mean duration of sexually active years	Mean number of intercourses per month
	abs	%			
Always	29	4.3	29.7±2.1	7.7±0.8	19.7±1.4
Often	173	25.6	30.3±1.9	6.8±0.6	16.8±1.5
Rare	265	39.2	32.5±2.4	9.8±1.0	14.6±1.3
Never	209	30.1	34.4±2.5	11.2±1.2	12.2±0.9
Total	676	100	31,7±2.2	8.9±0.9	15.8±1.3

Assessment of orgasms in different groups revealed a significant prevalence of anorgasm in groups I and II, compared to the III group.

Table 2. Assessment of orgasm according to groups.

Orgasm	I group		II group		III group		P1	P2	P3
	abs.	%	abs.	%	abs.	%			
Always	3	2.0	5	4.0	21	5.2	$P < 0.01$	$P < 0.01$	$P < 0.05$
Often	9	6.1	16	12.8	148	36.7	$P < 0.01$	$P < 0.01$	$P < 0.01$
Rarely	31	20.9	55	44.0	179	44.4	$P < 0.01$	$P < 0.01$	$P > 0.05$
Never	105	70.9	49	39.2	55	13.6	$P < 0.01$	$P < 0.01$	$P < 0.01$
Total	148	100	125	100	403	100			

P1 – difference between I gr and II gr

P2 – difference between I gr and III gr

P3 – difference between II gr and III gr

There were no statistically significant differences ($P>0.05$) in any group between the frequencies of grades of libido.

Table 3. Assessment of libido according to groups.

Libido	I group		II group		III group		P1	P2	P3
	abs.	%	abs.	%	abs.	%			
Low	49	33.1	44	35.2	140	34.7	$P>0.05$	$P>0.05$	$P>0.05$
Medium	63	42.6	57	45.6	168	41.7	$P>0.05$	$P>0.05$	$P>0.05$
High	36	24.3	24	19.2	95	23.6	$P>0.05$	$P>0.05$	$P>0.05$
Total	148	100	125	100	403	100			

P1 – difference between I gr and II gr

P2 – difference between I gr and III gr

P3 – difference between II gr and III gr

Sexological evaluation of women according to groups

In the I group (women with ovarico-varicocele), the rate of women with anorgasmia (70,9%) and rare orgasms (20,9%) was significantly higher ($P<0.01$) than the rate of women who had orgasms often (6,1%) or always (2,0%).

As of relationship between intensity of sexual drive (libido) and frequency of orgasms – there was direct dependence – women with anorgasmia (70,9%) and rare frequency of orgasms (20,9%) mainly had low (38,7-41,9%) or medium (35,2-43,8%) libido and in women, who had orgasms often (6,1%) or always (2,0%) libido was mainly medium (44,4-55,6%) or high (100%).

Table 4. Sexological evaluation of women in the I group.

Orgasm	Number of women		Libido low		Libido medium		Libido high	
	abs.	%	abs.	%	abs.	%	abs.	%
Always	3	2.0					3	100
Often	9	6.1			4	44.4	5	55.6
Rarely	31	20.9	12	38.7	13	41.9	6	19.4
Never	105	70.9	37	35.2	46	43.8	22	21.0
Total	148	100	49		63		36	

In the II group (women with dilatation of myometrium veins), the rate of women with anorgasmia (39,2%) and rare orgasms (44,0%) was significantly higher ($P<0.01$) than that of women who had orgasms often (12,8%) or always (4,0%).

As of relationship between intensity of sexual drive (libido) and frequency of orgasms – in this group also there was direct dependence – women with anorgasmia (39,2 %) and rare frequency of orgasms (44,0 %) mainly had low (20,0-59,2%) or medium (40,8-52,7%) libido and in women, who had orgasms often (12,8%) or always (4,0%) libido was mainly medium (20,0-43,8%) or high (20,0-80,0%).

Table 5. Sexological evaluation of women in the II group.

Orgasm	Number of women		Libido low		Libido medium		Libido high	
	abs.	%	abs.	%	abs.	%	abs.	%
Always	5	4.0	0	0	1	20	4	80
Often	16	12.8	4	25.0	7	43.8	5	31.3
Rarely	55	44.0	11	20.0	29	52.7	15	27.3
Never	49	39.2	29	59.2	20	40.8	0	0
Total	125	100	44		57		24	

In the III group, we generally observed prevalence of women without absolute absence or presence of orgasms – the rate of women, who had orgasms often (36,7%) or rarely (44,4%) was significantly higher ($P<0.01$) than women, who had orgasms always (5,2%) or never (13,6%).

As of relationship between intensity of sexual drive (libido) and frequency of orgasms – in this group also there was direct dependence, but not so expressed as in I and II groups – women with anorgasmy (13,6 %) and rare frequency of orgasms (44,4 %) mainly had low (41,9-49,1%) or medium (23,6-45,3%) libido and in women, who had orgasms often (36,7%) or always (5,2%) libido was mainly medium (14,3-48,0%) or high (26,4-85,7%).

Table 6. Sexological evaluation of women in the III group.

Orgasm	Number of women		Libido low		Libido medium		Libido high	
	abs.	%	abs.	%	abs.	%	abs.	%
Always	21	5.2	0	0	3	14.3	18	85.7
Often	148	36.7	38	25.7	71	48.0	39	26.4
Rarely	179	44.4	75	41.9	71	45.3	23	12.8
Never	55	13.6	27	49.1	13	23.6	15	27.3
Total	403	100	140		168		95	

Discussion

Study results provide a fruitful field for analysis and discussion. Prevalence of anorgasmy and rare frequency of orgasms in women with OVVC and DMV might be considered as evidence of the causal influence of anorgasmic coitus on the development of congestive processes in the small pelvis, with further development of varicose changes of ovarian veins and dilatation of myometrium veins. In itself, OVVC and DMV might be suitable bases for amplification of other gynecological pathologies and conditions.

Ovarian varicose veins characterize themselves in the form of dilated, tortuous, and congested veins next to the ovarian gland, often causing chronic pelvic pain and a feeling of heaviness in the pelvis in women.^{13,14}

Several studies have demonstrated that over 50% of patients with ovarian varicose veins have polycystic ovaries,^{15,30} and that the morphologic and functional changes in the polycystic ovary syndrome increase the risk of cancer,^{16,18} venous thrombosis,^{17,18} infertility, and cardiovascular problems,¹⁹ as well as decreasing the ovarian reserve.¹⁶

Increased oxidative stress (OS) in varicose dilations provokes histological damage in the ovaries and suggests an adverse effect related to fertility.²⁰ Moreover, researchers have also evidenced that female infertility may increase the risk of cancer and other pathologies.^{21,22}

Some authors have demonstrated the frequency of ovarian varicose veins in women by pathology: in women who suffered from chronic pelvic pain, the prevalence was 50%^{23,24}, in women with endometriosis, the prevalence was 80%²⁵, in women who had endometriomas in the left ovary, the prevalence was 100%.²

The therapeutic test suggests that varicose veins cause destruction of tissue and organs, OS in endothelial cells, and, as a result of these damages, the alteration of the expression of several genes.²⁷⁻²⁹

Congestive processes in the pelvis can influence varicose dilatation of pelvic veins, including myometrium veins,^{30,31} which might be complicated with thrombosis, development of cystic and malignant formations.^{32, 33}

Congestive processes and varicose of ovarian or pelvic veins often are causes of chronic pelvic pain,^{34,35} which in turn can influence orgasmic functions and determine anorgasm.

Summarizing all the above-mentioned, we can conclude that orgasmic dysfunctions (anorgasm) can promote a congestive process in the pelvis, development of varicosis of ovarian and pelvic veins (with corresponding other gynecological complications), which themselves can determine chronic pelvic pain that deepens the anorgasmic process. So, a locked, vicious circle is forming, and the only strategy to manage this situation is a complex approach for treating all components and conditions. Also, in younger ages and early stages of the beginning of sexual life, timely management of anorgasm might be a good prevention for further development of gynecological pathologies.

Conclusions

Orgasmic dysfunctions (anorgasm) can promote a congestive process in the pelvis, development of varicosis of ovarian and pelvic veins (with corresponding other gynecological complications), which themselves can determine chronic pelvic pain that deepens the anorgasmic process.

In younger ages and early stages of the beginning of sexual life, timely management of anorgasm might be a good prevention for further development of gynecological pathologies.

The issue requires further investigation to reveal the cause-and-effect relationship.

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EFFECT OF MENOPAUSE ON VITAMIN D DEFICIENCY AND COVID-RELATED HEALTH OUTCOMES IN THE FEMALE POPULATION OF GEORGIA

NIA METONIDZE, MD, PhD

Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Vitamin D deficiency was highly prevalent in female patients hospitalized due to COVID-19. Elderly female patients are characterized by higher values of hospitalization and lower values of survival.

Objective: This study aimed to evaluate the effect of menopause on vitamin D deficiency and COVID-related health outcomes (hospitalization, transfer to ICU unit, requirement of oxygen therapy, and treatment with glucocorticoids).

Materials and Methods: A retrospective cross-sectional study was conducted, based on the data of the National Center for Disease Control and Public Health (NCDC) of Georgia. After obtaining the written informed consent, 291 persons registered in the NCDC database have been included in the study group. Study's female subjects were divided into two age groups: group 1 – patients with menopause – n=123; group 2 – patients without menopause, n=168.

Results: Mean levels of serum 25(OH)D in the study groups did not differ significantly. But these values were significantly lower in hospitalized female patients of both groups. The odds of hospitalization and oxygen therapy in group 1 were significantly higher compared to group 2. The odds of transfer to the ICU unit and treatment with glucocorticoids between the groups were not significant.

Conclusions: Our study revealed significantly worse COVID-19-related health outcomes in patients with menopause compared to patients without menopause. Moreover, the difference between the mean 25(OH)D levels of hospitalized and non-hospitalized patients of both age groups was statistically significant. However, the effect of menopause on the mean 25(OH)D levels was not revealed.

Keywords: COVID-19; elderly; health outcomes; hospitalization; vitamin D

Introduction

The COVID-19 pandemic was the outbreak following SARS in 2002 and MERS infections in 2012.¹⁻² However, in contrast to previous ones, COVID-19 has higher transmission rates. It thus incurs more challenges in terms of prevention and treatment.² Mortality and other complications were the most susceptible adverse outcomes from COVID-19.³ Their risk also increases

in the presence of multiple comorbidities such as diabetes, cardiovascular disease, respiratory disease, malignancy, and obesity.³⁻⁶

SARS-CoV-2 infection induces local and systemic inflammatory responses in humans.⁷ Inflammation accompanied by an exaggerated immune response leads to pyroptosis, tissue damage in patients with COVID-19.⁸ When SARS-CoV-2 infects the lungs, it causes alveolar epithelial cell death, endothelial disruption, increased lung permeability, and alveolar edema, and can lead to acute respiratory distress syndrome (ARDS) and multiorgan failure.⁹

In patients hospitalized for COVID-19, vitamin D deficiency was highly prevalent.¹⁰ Therefore, it is rational to assume a beneficial role of vitamin D supplementation in preventing, reducing symptoms, or improving the prognosis of this disease. Several dozen studies have been conducted to determine the effect of vitamin D on COVID-19. Among them, a few have found promising results. A RCT of oral vitamin D3 (cholecalciferol; 60,000 IU daily), with a therapeutic target of serum 25(OH)D > 50 ng/mL, was found to significantly induce negative conversion of SARS-CoV-2-RNA and lead to a decrease in fibrinogen levels.¹¹ Other small-scale studies have also shown that vitamin D supplementation during or in the month preceding SARS-CoV-2 infections was associated with less severe outcomes, including lower mortality, even in elderly patients.¹² Asymptomatic or mildly symptomatic patients with COVID-19 given vitamin D showed improvement in associated symptoms on day 14, but did not significantly reduce the time to negative transformation of SARS-CoV-2 RNA virus.¹³ Another study found that a single high dose (200,000 IU) of vitamin D did not reduce the length of hospital delay or mortality in patients hospitalized for moderate to severe COVID-19.¹⁴ Elderly patients survived after COVID-19, but it took more time for them to fully recover compared to other age groups. The outcome of these conditions was rapid loss of muscle mass after hospital discharge due to immobilization, which can increase the risk of frailty, falls, fractures, and mortality.¹⁵

Therefore, our study aimed to investigate the age peculiarities of vitamin D deficiency and COVID-related health outcomes (hospitalization, transfer to ICU unit, requirement of oxygen therapy, treatment with glucocorticoids).

Study Design and Subjects

A retrospective cross-sectional study was performed based on the data of the National Center for Disease Control and Public Health (NCDC) of Georgia. Three hundred thirty-five records of the patients with determined serum 25-hydroxyvitamin D [25(OH)D] levels were randomly selected for the study. Researchers provided the visits of these patients, and after obtaining the written informed consent, 291 persons registered in the NCDC database were included in the study group.

Study Parameters

The data on hospitalization, its duration, transfer to the ICU unit, requirement of oxygen therapy, treatment with glucocorticoids, and symptoms were extracted from the NCDC database. The patients were surveyed using specially structured questionnaires to gather information on their vitamin D supplementation status prior to SARS-CoV-2 confirmation.

Study Groups

Study subjects were divided into two age groups: group 1 – patients with menopause, n=123; group 2 – patients without menopause, n=228.

Statistical Analysis

The study results were statistically analyzed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean standard deviation (SD), and differences were assessed by analysis of variance. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Odds ratios (ORs) and 95% CIs within the presented study were estimated. P values of <0.05 were considered statistically significant.

Study Characteristics

The age, body mass index (BMI) data, and the distribution by gender and body weight status of the patients in the study groups are given in Table 1.

Table 1. Age, BMI, and the distribution of patients by gender and body weight status in the study groups.

#	Parameter	Group 1 (n=123)		Group 2 (n=168)	
		Mean	SD	Mean	SD
1	Age, years	63.5	8.0	29.2	9.9
2	BMI, kg/m ²	27.2	3.7	24.3	4.4
3	Body Weight Status	n=	%	n=	%
	Normal	31	25.2%	103	61.3%
	Overweight	67	54.5%	45	26.8%
	Obesity	25	20.3%	20	11.9%

It is clear from the table that BMI mean values differed significantly between the groups (t-test=5.93, $p<0.001$). The same trend was found in the distribution by body weight status between the groups – chi2-test = 37.50, df=2, $p<0.001$.

Mean levels of serum 25(OH)D in the study groups are given in Chart 1. The difference of these values between the groups was not significant - $t=0.773$, $p=0.440$.

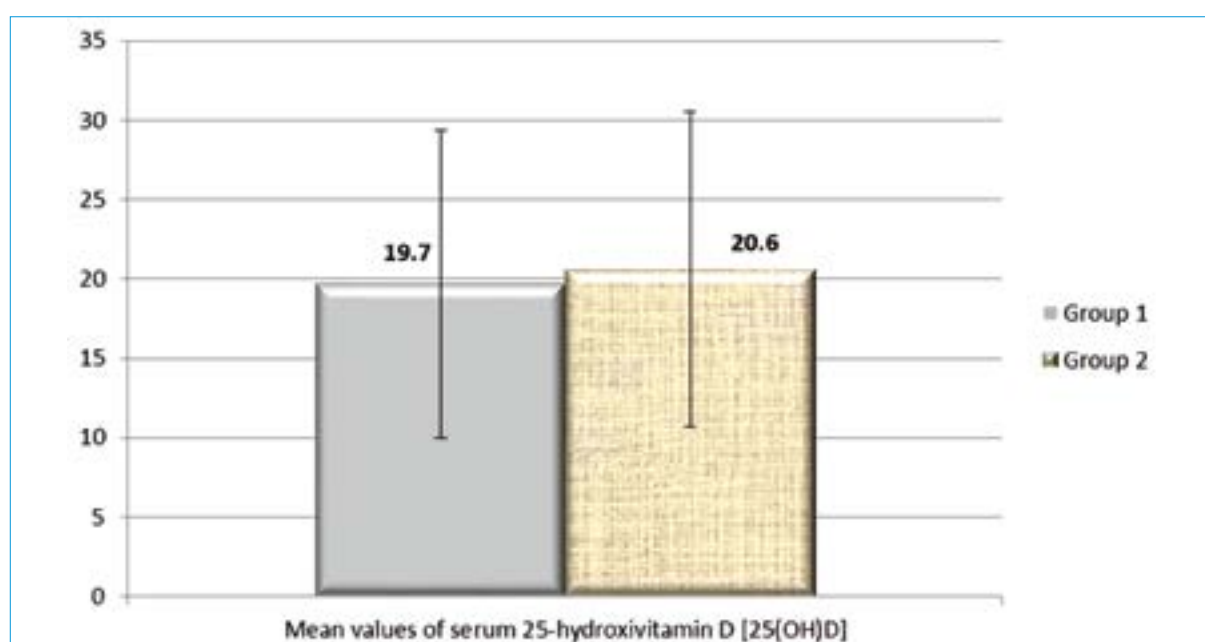


Chart 1. Mean levels of serum 25-hydroxyvitamin D [25(OH)D].

The data on rates of hospitalization, transfer to ICU unit, the requirement of oxygen therapy, the treatment by glucocorticoids, and SARS-Cov-2 infection symptoms were extracted from the NCDC database are given in Table 2.

Table 2. The distribution of patients by the rates of hospitalization, transfer to the ICU unit, the requirement of oxygen therapy, the treatment by glucocorticoids, and SARS-infected symptoms in the study groups.

#	Health outcomes	Group 1 (n=123)		Group 2 (n=168)	
		n=	%	n=	%
1	Hospitalization	23	18.7%	10	6.0%
2	Transfer to the ICU unit	2	1.6%	2	1.2%
3	Requirement of oxygen therapy	11	8.9%	4	2.4%
4	Treatment with glucocorticoids	7	5.7%	4	2.4%

The odds of hospitalization and the requirement of oxygen therapy in group 1 were significantly higher compared to group 2 (OR = 3.63, $p=0.001$; OR = 4.03, $p=0.020$, respectively). The odds of the requirement of transfer to the ICU unit (OR = 1.37, $p=0.754$), and the treatment by glucocorticoids (OR = 2.47, $p=0.156$) between the groups were not significant.

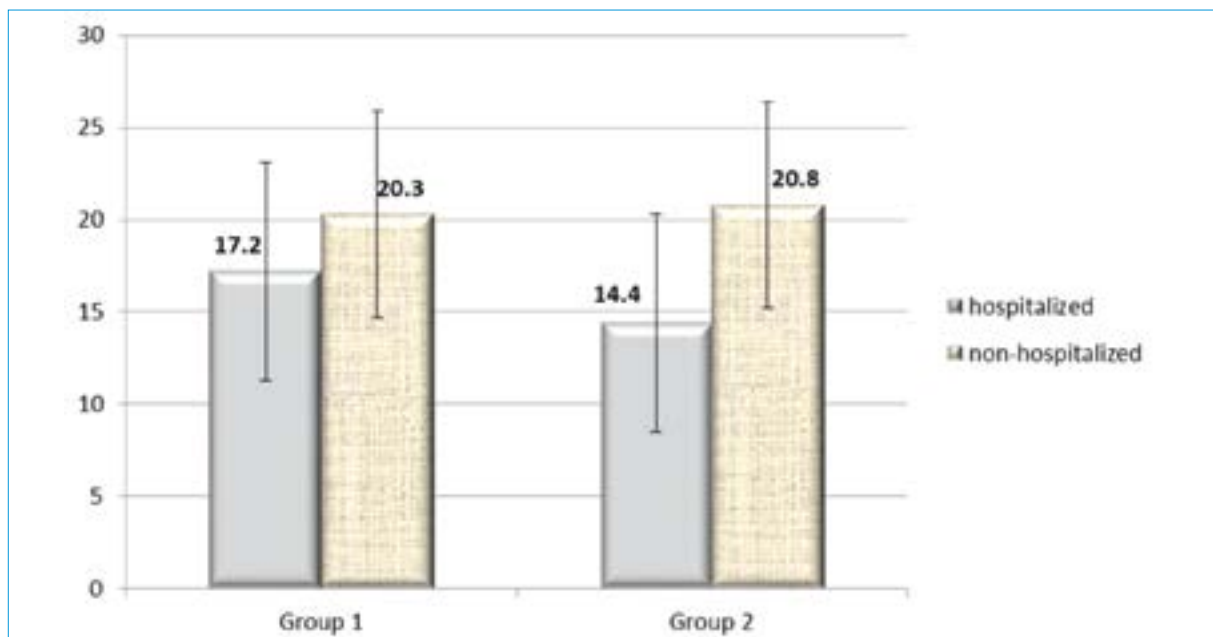


Chart 2. Mean levels of serum 25-hydroxyvitamin D [25(OH)D] in hospitalized and non-hospitalized patients in both groups.

Mean levels of serum 25-hydroxyvitamin D [25(OH)D] in hospitalized patients were significantly lower in both groups compared to non-hospitalized patients ($p<0.05$). However, the difference in these levels between the groups of hospitalized patients was not significant ($p>0.05$).

Discussion

There has been a lot of discussion about the impact of vitamin D on SARS-COV-2 infection. Vitamin D may alter the disease manifestations depending on its influence on macrophage

function and innate immunity. Vitamin D supplementation becomes relevant in the absence of highly effective prevention and treatment strategies for the pandemic. Considering the availability and economic pricing of drugs, especially in developing countries (countries of Group A and B by the Research4Life program),¹⁶ vitamin D supplementation should be an important option for the populations at risk.

Previous systematic reviews have clearly shown an inverse association between 25(OH)D concentration and acute respiratory tract infections,^{8,17} but these studies were not directly focused on SARS-CoV-2 infection. Similar to our findings, a study from the UK by Panagiotou et al. found that low serum 25(OH)D levels in 134 hospitalized patients with COVID-19 were associated with a more severe disease course.¹⁸

Conversely, a study using the UK Biobank looked at 348 598 participants, of whom only 449 had a confirmed diagnosis of COVID-19 as defined by a positive laboratory test for SARS-CoV-2 (only 0.13% of the study population). They did not find any association between 25(OH)D and risk of COVID-19 infection.¹⁹ In addition to the low number of patients with COVID-19, other weaknesses in this study included heterogeneity in severity and management of COVID-19 cases (likely a mixture of inpatient and community, instead of focusing on COVID-19 cases in only one setting), serum 25(OH)D measurement between 2006 and 2010, and not contemporaneously with COVID-19 infection 10 to 14 years after recruitment to the UK Biobank, and no mention of validation of 25(OH)D measurement.

In terms of 25(OH)D and COVID-19 disease severity, a study from India of 154 patients admitted to hospital with COVID-19 reported that the mean 25(OH)D level was <30 ng/mL (insufficient range), and patients admitted to the intensive care unit and those that died from COVID-19 were more deficient in vitamin D than survivors.²⁰ Another study from Belgium (n = 186) reported similar findings of greater deficiency rates in patients with more severe disease.²¹ Similarly, a study from Switzerland demonstrated that 25(OH)D concentrations were significantly lower in patients with COVID-19 than in those without the disease.²²

Other studies have also demonstrated a correlation between vitamin D deficiency and COVID-19 infection, contrary to the study using patients from the UK Biobank. A study from Israel with 7807 subjects demonstrated that 25(OH)D concentrations were significantly lower among those who tested positive for COVID-19 than those who were COVID-19 negative.²³ A study from Wuhan, China, showed in a multivariable logistic regression that vitamin D deficiency (<30 nmol/L) was significantly associated with COVID-19 severity.²⁴

It has long been clear that groups that traditionally exhibit vitamin D deficiency or insufficiency, such as older adults and nursing home residents, and Black, Asian, and minority ethnic populations, are the same groups that COVID-19 has disproportionately impacted. Additionally, increased time spent indoors due to strict lockdowns and shielding triggered concerns that some people might not obtain the necessary physiological levels of vitamin D from sunlight.²⁵

Conclusion

Our study revealed significantly worse COVID-19-related health outcomes in patients with menopause compared to patients without menopause. Moreover, the difference between the mean levels of serum 25-hydroxyvitamin D [25(OH)D] of hospitalized and non-hospitalized patients of both age groups was statistically significant. However, the effect of the menopause on mean levels of serum 25-hydroxyvitamin D [25(OH)D] was not revealed.

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FROM NEAR MISS TO NEVER AGAIN: TWO DECADES OF RISK MANAGEMENT AND ERROR PREVENTION IN AN IVF LABORATORY

MARINA GVAKHARIA, MD, PhD

HCLD/ELD(ABB), CLS(CA), MT(ABOR) Palo Alto Medical Foundation, Palo Alto, California, USA

ABSTRACT

Objective: To evaluate 20-year outcomes of a structured quality improvement (QI) and risk-management program in a single IVF laboratory, with emphasis on never events, near misses, and longitudinal performance on predefined quality indicators (QIIs).

Design: Longitudinal, single-center quality improvement study (2004–2024).

Setting: Large healthcare network -affiliated IVF laboratory operating under CAP accreditation.

Patients/Cycles: 15,956 ART cycles (8,320 fresh IVF; 7,636 frozen embryo transfer).

Interventions: Implementation and continuous refinement of a laboratory QI framework comprising high-risk process mapping; QIIs with thresholds; standardized reporting (verbal escalation → SBAR); structured investigations (RCA) with corrective/preventive actions (CAPA); competency-based staff training; electronic/dual witnessing; cryoinventory reconciliation; equipment maintenance and alarm testing; and a non-punitive reporting culture.

Main Outcome Measures: Incidence of never events and intercepted near misses; protocol non-compliance; report errors; cryoinventory accuracy (QIR07); gamete/embryo traceability (QIR10); equipment/handling issues affecting care (QIR16).

Results: Across 20 years, one true “never event” occurred (erroneous discard of an embryo intended for cryopreservation with freezing of a lower-quality embryo instead; ≈0.006% of cycles). The event was disclosed, investigated via RCA, corrected per SOPs, and remediated with a no-cost IVF cycle. One intercepted near miss (thaw of an undesired-gender embryo detected pre-transfer) was identified, disclosed, and resolved (refreeze and correct embryo transfer) without clinical impact. Protocol non-compliance declined from 8 cases (2004) to 0 by 2008 and remained at or near zero thereafter. Report errors decreased to 0% in recent years. Cryoinventory performance remained near 0% error with one easily resolved misplacement. Gamete/embryo traceability (QIR10) stayed well below thresholds with no significant missing/untraceable specimens. QIR16 recorded one handling incident (faulty pipette), causing loss of several oocytes, prompting protocol revision, equipment checks, and retraining via RCA/CAPA.

Conclusions: A structured, data-driven QI program—embedding SBAR, RCA/CAPA, traceability safeguards, and a just culture—was associated with sustained near-zero serious events and progressive reliability gains over two decades. This reproducible model can inform benchmarking and multi-center learning aimed at further reducing latent risk in IVF laboratories.

Keywords: In vitro fertilization (IVF) laboratory; Quality improvement (QI); Patient safety; Never events; Root cause analysis (RCA); Corrective and preventive actions (CAPA); Specimen traceability and cryoinventory.

Introduction

In vitro fertilization (IVF) is a highly complex medical process that requires seamless coordination between the clinical, surgical, and laboratory components of care [1,2]. The success of an IVF cycle hinges not only on advanced medical and embryological techniques but also on the precision, vigilance, and reliability of each team involved. Within the IVF laboratory in particular, stringent procedural controls and quality assurance measures are essential to prevent errors that, while rarely life-threatening, can have profound emotional and clinical consequences for patients [1]. In this paper, we present our experience implementing a robust internal risk management and error prevention program at a single IVF center over a 20-year period. We describe the evolution of our systems, the types of nonconformances encountered, and the strategies that proved most effective in fostering a culture of safety, accountability, and continuous improvement.

Materials and Methods

In compliance with the College of American Pathologists (CAP) laboratory accreditation standards, our IVF laboratory established a comprehensive Quality Improvement (QI) program aimed at identifying, monitoring, and mitigating risks throughout all phases of laboratory operations [3,4]. A key component of this initiative was the systematic identification of high-risk process steps where nonconformances were most likely to occur, and the mapping of performance indicators to those steps [2].

For each identified risk point, we developed corresponding Quality Improvement Indicators (QIIs) and established predefined threshold limits, informed by historical performance metrics, clinical significance, and regulatory guidance [2–4]. These QIIs served as measurable benchmarks for ongoing monitoring and quality assessment. A complete list of QIIs and their respective thresholds is provided in Table 1.

Nonconformances were broadly defined to include, but not be limited to, documentation errors, specimen mislabeling, procedural deviations, equipment failures, and any departure from standard operating procedures (SOPs). The reporting process began with an immediate verbal notification to the supervisor or laboratory director, followed by discussion during the daily laboratory huddle.

Following this, a written SBAR (Situation, Background, Assessment, Recommendation) report was submitted by the staff member involved [5]. When necessary, a structured root cause analysis (RCA) was conducted to understand the underlying factors contributing to the event fully and to guide the development of appropriate corrective and preventive actions (CAPA) [6].

All nonconformance reports were logged into a centralized database (Figure 1) and reviewed during regular laboratory meetings. Staff were trained to report all deviations in a non-punitive environment, reinforcing a culture of transparency, safety, and continuous improvement [6].

Nonconformance incidents were tracked and plotted on a monthly basis, allowing for trend analysis and early detection of recurring issues. The effectiveness of the QI program was evaluated annually by comparing current data against the laboratory's historical benchmarks, in alignment with CAP accreditation requirements [3,4].

Additionally, "never events" were defined as serious, clearly identifiable, and largely preventable incidents that compromise patient identity, consent, genetic parentage, or the integrity of gametes/embryos—i.e., events that must not occur if clinic systems and controls are functioning as designed (Table 2) [7,8].

Results

In the interest of brevity, we present a sample of key performance indicators observed over the study period.

Never Events:

Over the course of 20 years, our program performed 8,320 fresh IVF cycles and 7,636 frozen embryo transfer (FET) cycles. Within this period, two significant adverse events were documented.

1) True Never Event

Incident: An embryo intended for cryopreservation was erroneously discarded, while a lower-quality embryo was frozen in its place.

Response: A full Root Cause Analysis (RCA) was conducted in accordance with established SOPs. Corrective actions were implemented, and the affected patient was offered a repeat IVF cycle at no cost.

2) Intercepted Never Event

Incident: An embryo of an undesired gender was mistakenly thawed.

Response: The issue was identified prior to embryo transfer. The patient was immediately informed, the embryo was refrozen, and the correct embryo was thawed and transferred without clinical impact.

Quality Indicators (2004-2024):

One of the most impactful trends observed was the elimination of protocol non-compliance. Specifically, the number of documented deviations from laboratory protocols decreased from 8 cases in 2004 to 0 by 2008, remaining at or near zero thereafter (Figure 2).

Report accuracy improved steadily due to safeguards including routine audits, dual-signature protocols, structured proofreading, and electronic verification systems, reaching 0% documented errors in recent years (Figure 3).

Cryopreserved specimen tracking (QIR07) performed near 0% error across the period; one misplaced specimen was rapidly identified and resolved without patient impact, supported by labeling, reconciliation audits, dual-operator verification, and secure tank mapping.

Gamete/embryo traceability (QIR10) remained well below thresholds with no significant missing or untraceable specimens, supported by chain-of-custody controls, redundant witnessing, periodic audits, and cryostorage reconciliation.

Technical difficulties with equipment or handling (QIR16) included a single incident caused by a faulty pipette, resulting in the loss of several oocytes. This incident prompted protocol revisions, equipment checks, and retraining, which were executed via RCA/CAPA.

Overall, quality indicators remained low throughout the 20-year study period and either improved or remained at predefined acceptable thresholds.

Discussion

Principal findings

Over 20 years and 15,956 ART cycles, a structured QI program—anchored in proactive monitoring, standardized reporting (verbal notification → SBAR → RCA → CAPA), and a non-punitive safety culture—was associated with sustained low rates of nonconformance and continued improvement across key indicators [2,3,5,6,12]. Only one true never event occurred (erroneous discard of an embryo intended for cryopreservation with freezing of a lower-quality embryo instead), and one intercepted near miss was identified before reaching the patient (thaw of an undesired-gender embryo detected pre-transfer) [7,8].

Interpretation

In IVF, where errors can carry profound emotional, ethical, and legal consequences despite rarely threatening physical safety, the bar for identity verification, documentation integrity, and specimen traceability is uniquely high [1,7]. The elimination of protocol non-compliance within four years, the decline of report errors to zero, and near-zero rates for cryo-inventory and traceability issues suggest that program controls reduced latent system risk [1–3,9–11]. The single handling incident linked to a faulty pipette demonstrates how isolated events can catalyze durable system improvements (protocol revision, equipment checks, retraining) [6].

Key program elements

Outcomes likely reflect: (1) early identification of high-risk steps; (2) clearly defined QI indicators with explicit thresholds; (3) immediate, standardized response workflows (verbal escalation, SBAR, RCA, CAPA); (4) routine trend review with feedback to staff; (5) a just culture that encourages reporting; and (6) visible leadership engagement [2–6,12].

Strengths and limitations

Strengths include the long observation period, consistent definitions of nonconformance, and closed-loop corrective actions. Limitations include the single-center design, potential under-reporting bias inherent to incident-driven systems, and evolving case mix, technology, and staffing over two decades that may confound temporal trends. Thresholds were tailored to local risk tolerance and may require calibration before external adoption [2–4].

Implications for practice

Embedding QI into day-to-day operations—rather than treating it as a periodic audit—appears essential. Laboratories seeking similar outcomes should prioritize identity-check redundancy, cryoinventory reconciliation, structured documentation reviews, and rapid RCA/CAPA cycles; electronic or automated witnessing can support efficiency and reduce risk [1,2,9–11]. Patient-centered transparency (including timely disclosure and remediation) is both ethically imperative and operationally clarifying [7].

Future directions

Multi-center collaborations using harmonized indicators, electronic witnessing/traceability analytics, and prospective evaluation of near-miss data could refine benchmarks and accelerate learning across programs [2,9–11].

Summary

Across two decades, a robust, data-driven quality management program in a single IVF laboratory was associated with one true never event, one intercepted near miss, and sustained improvement of critical metrics—protocol non-compliance to zero, report errors to zero in recent years, and near-zero rates for cryoinventory and traceability issues—while a single handling incident prompted comprehensive protocol and training reforms [1–3,6–11]. These results support a reproducible model in which measurable indicators, timely reporting, structured RCA/CAPA, and a supportive safety culture jointly uphold patient safety and the integrity of IVF processes.

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Table 1. IVF laboratory QI program: Quality indicators, thresholds, and corrective actions

Quality Indicator	Threshold	Corrective action
QIR01 – Lab protocol non-compliance (including near misses) (# non-compliance / # ART procedures × 100%)	0%	SBAR; +/- direct observation; RCA; Implementation as needed
QIR02 – Laboratory communication issue	≤3 episodes/month	SBAR; RCA; Implementation as needed
QIR03 – Consent issue (incomplete, missing info/ form)	≤2 episodes/month	SBAR; RCA; Implementation as needed
QIR04 – Requisition form issue (incomplete, missing info/ form)	≤2 episodes/month	SBAR; RCA; Implementation as needed
QIR05 – Error in released report (# occurrence / # ART procedures × 100%)	<5%	SBAR; RCA; Implementation as needed
QIR07 – Cryoinventory issue (e.g., missing or misplaced specimens)	0%	SBAR; RCA; Implementation as needed
QIR08 – Scheduling issue affecting or potentially affecting patient care	0%	SBAR; RCA; Implementation as needed
QIR09 – Chain of custody not documented	0%	SBAR; RCA; Implementation as needed
QIR10 – Missing eggs / embryos (# missing / # handled × 100%)	≤2%	SBAR; RCA; Implementation as needed
QIR13 – Incomplete forms / document control issue by the clinic	≤3/month	SBAR; RCA; Implementation as needed
QIR14 – Incomplete forms by MD	≤3/month	SBAR; RCA; Implementation as needed
QIR15 – Incomplete forms by IVF lab	≤3/month	SBAR; RCA; Implementation as needed

QIR16 – Technical issue affecting laboratory procedure (e.g., oocytes stuck in stripper; difficulty loading transfer catheter)	<2/month	SBAR; +/- direct observation; RCA; Implementation as needed
QIR17 – Procedure not performed as requisitioned	0%	SBAR; RCA; Implementation as needed
QIR20 – FDA compliance issue	0%	SBAR; RCA; Implementation as needed
QIR21 – Media/dish/chart preparation issue (near miss or actual problem)	0%	SBAR; +/- direct observation; RCA; Implementation as needed
QIR22 – QC procedure not performed per schedule/no corrective action performed	0%	SBAR; RCA; Implementation as needed
QIR23 – Identification and/or labeling issue	0%	SBAR; RCA; Implementation as needed
QIR24 – Report turnaround time not met	4 reports/month	SBAR; RCA; Implementation as needed
QIR25 – Equipment failure affecting culture system	0%	SBAR; RCA; Implementation as needed
QIR26 – HIPAA issue (patient confidentiality)	0%	SBAR; RCA; Implementation as needed
QIR27 – OSHA issues (workplace injury, biohazard/chemical exposure, other safety concerns)	0	SBAR; RCA; Implementation as needed
QIR28 – Bacterial contamination of culture (from semen sample or other source)	0	SBAR; RCA; Implementation as needed
QIRC29 – Clinical/ASC issues that can affect laboratory/outcomes	0	SBAR; RCA; Implementation as needed
QIRC30 – Complaints (patient/physician/colleagues)	0	SBAR; RCA; Implementation as needed

Table 2. IVF laboratory QI program: Never Events and Corrective Actions

Never Event	Description	Corrective Actions (with RCA)
Wrong-patient / wrong-specimen use	Fertilization, insemination, culture, cryopreservation, thaw, or embryo transfer involving the incorrect gametes or embryos	1. Stop procedure immediately and secure specimens2. Notify laboratory and medical leadership immediately3. Inform affected patient(s) promptly4. Conduct urgent RCA and report to regulatory/ oversight bodies5. Revise SOPs, retrain staff, and strengthen identity-check systems
Procedure without valid consent	Any insemination, thaw, discard, transfer, or storage performed without documented and verified patient consent	1. Stop action immediately2. Notify laboratory and medical leadership immediately3. Inform patient(s) and disclose error4. Conduct RCA to identify gaps in the consent process5. Revise consent verification workflows and retrain staff
Irretrievable loss of gametes/embryos due to preventable error	Destruction or loss due to tank failure, ignored alarms, mislabeling, or incorrect warming/ handling	1. Secure and document affected material2. Notify laboratory and medical leadership immediately3. Inform patient(s) promptly4. Conduct RCA, including equipment/system review5. Update preventive maintenance protocols and retrain staff
Specimen released to the wrong recipient	Gametes or embryos given to the wrong patient, courier, or facility	1. Attempt immediate retrieval if possible2. Notify laboratory and medical leadership immediately3. Inform affected patient(s)4. Conduct urgent RCA and file regulatory reports as required5. Strengthen chain-of-custody and labeling SOPs and retrain staff

Inability to locate the cryopreserved specimen	Failure to find a stored gamete or embryo in the cryoinventory system (mislabeling, misplacement, or tracking error)	1. Suspend any planned procedures until resolved 2. Notify laboratory and medical leadership immediately 3. Inform affected patient(s) 4. Conduct an urgent RCA and perform a full cryoinventory audit 5. Improve reconciliation/audit procedures and retrain staff
Patient's concerns about the parentage of a pregnancy or baby	A patient raises concern that a pregnancy or live birth may not be genetically theirs (suspected specimen mix-up or misattributed parentage)	1. Take concerns seriously and document in detail 2. Notify laboratory and medical leadership immediately 3. Inform compliance/risk management 4. Conduct urgent RCA, offer genetic testing and counseling, and report if confirmed 5. Strengthen identity verification and witnessing protocols

REPORT		JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	threshold
QIR01	Lab protocol non-compliance issue (0)													0
QIR02	Lab - communication issue													<=3/month
QIR03	Consent issue (incomplete, missing info, missing form)													<=2/month
QIR04	Req. form issue (incomplete, missing info, missing form)													<=2/month
QIR05	Error in the released report													<5%
QIR07	Cryoinventory issue													0
QIR08	Scheduling issue													0
QIR09	Chain of custody not documented													0
QIR10	Missing eggs/embryos													<=2%
QIR13	Incomplete forms													<=3/month
QIR14	Incomplete forms by MD													<=3/month
QIR15	Incomplete forms by the IVF lab													<=3/month
QIR16	Technical issue													<2/month
QIR17	Procedure not performed as requisitioned													0
QIR20	FDA compliance issue													0
QIR21	Media, dish, chart prep issue													0
QIR22	QC procedure not performed per schedule/no													0
QIR23	ID and/or labeling issue													0
QIR24	QIR24 QI report - report turnaround time not met													<=4/month
QIR25	QIR25 QI report - equipment failure that affected the culture system													0
QIR26	QIR26 QI report - HIPAA issue													0

Figure 1. IVF laboratory QI program: Quality indicators, thresholds, and corrective actions

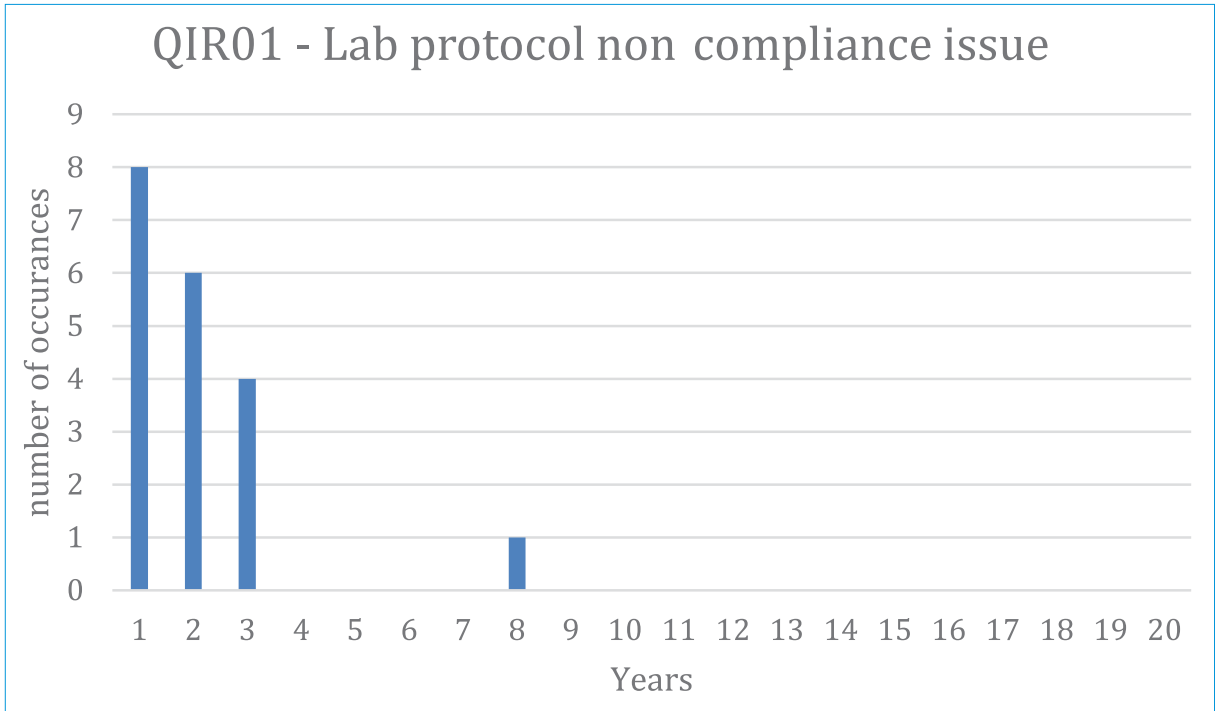


Figure 2. Performance of the QIR01 2004-2024

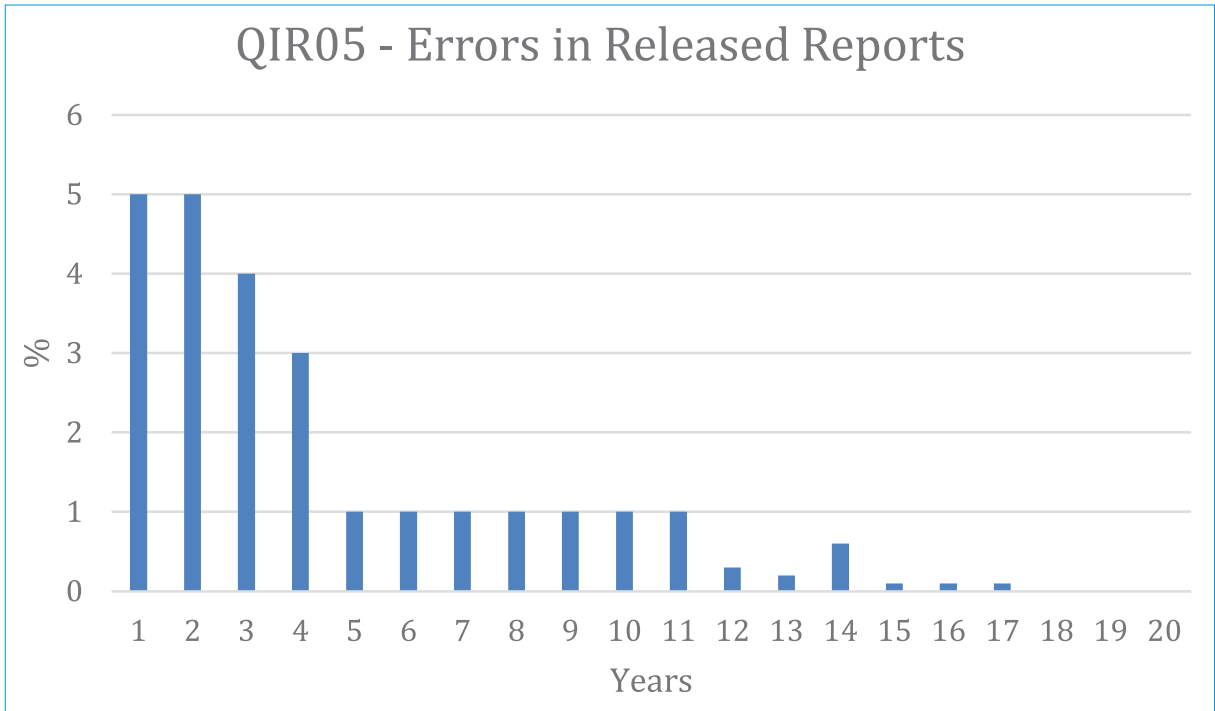


Figure 3. Performance of the QIR05 2004-2024

5th International Conference “Infertility 35+”
21-22 September, 2024, Tbilisi, Georgia

21/09/2024 Day 1 BALLROOM 1-2

09:00 – 10:00 | Registration

I SESSION
10:00 – 12:30 Chairman: Professor **ARCHIL KHOMASURIDZE**
Moderator: Professor **NINO MUSERIDZE**

10:00 – 10:10 | Opening ceremony. Welcome addresses
Professor **ARCHIL KHOMASURIDZE**
President of Georgian Association of Reproductive Health, Georgia

Professor **NINO MUSERIDZE**
Medical Director of Georgian-German Reproductology Center, Georgia

10:10 – 10:40 | The Future Trends of Human Reproduction
Professor **JOSEPH G. SCHENKER**
Chairman(Emeritus), Department Obstetrics and Gynecology,
Hebrew University -Hadassah Medical Center, Israel

10:40 – 11:10 | Maintaining Reproductive Options:
A Professional Imperative for Obstetrics and Gynecology
Professor **FRANK A. CHERVENAK**
Chair, Obstetrics & Gynecology Lenox Hill Hospital,
Associate Dean for International Medicine, USA

11:10 – 11:40 | The Fetal Factor in Recurrent Pregnancy Loss
Professor **HOWARD CARP**
Obstetrics and Gynecology, Tel Aviv University,
Sheba Medical Center, Israel

11:40 – 12:10 | Demographic Decline of Fertility 1900-2100
Professor **SEANG LIN TAN**
Origin Elle Fertility Clinic and Women's Health Centre, Canada

12:10 – 12:30 | Discussion

12:30 – 13:00 | Coffee break

II SESSION
13:00 – 14:40 Chairman: Professor **ARCHIL KHOMASURIDZE**
Moderator: Professor **NINO MUSERIDZE**

13:00 – 13:20 | Regenerative Medicine for Fertility
Professor **NINO MUSERIDZE**
Medical Director of Georgian-German Reproductology Center, Georgia

13:20 – 13:40 | Showing Potential Efficacy of Metabolic Compounds in Male Fertility
Professor **GIAN MARIA BUSETTO**
Associate Professor of Urology, University of Foggia, Italy

13:40 – 14:00 | Premature Ovarian Insufficiency, Determined by X Chromosome Anomalies

Professor **JENARO KRISTESASHVILI**

Department of Reproductology, Obstetrics and Gynecology,
Ivane Javakhishvili Tbilisi State University, Georgia

14:00 – 14:20 | *Discussion*

14:20 – 15:20 | *Coffee break*

III SESSION

Chairman: Professor **ARCHIL KHOMASURIDZE**

15:00 – 17:00

Moderator: Professor **NINO MUSERIDZE**

15:20 – 15:40 | Prostate Cancer and Preservation of Male Sexual Function -
Micro-Ultrasound 29MHz based Early Detection

Professor **GURAM KARAZANASHVILI**

President of Georgian Association of Oncological Urology, Georgia

15:40 – 16:00 | Gestational Diabetes Mellitus -from Risk Factors to Prevention

Professor **RAMAZ KURASHVILI**

Head, Department of Endocrinology, European University, Tbilisi

16:00 – 16:20 | Control of Hemostasis During Post-IVF Pregnancy

Professor **ALEXANDER MAKATSARIA**

Academician of the Russian Academy of Sciences

Head of the Department of Obstetrics, Gynecology and Perinatal medicine

16:20 – 16:40 | Endometrium – What? Where? When?

Professor **MADONA JUGELI**

Gynecologist-Endocrinologist, Head of the Office Gynecology Department,
Caraps Medline, Georgia

16:40 – 17:00 | Artificial Intelligence in Assisted Reproduction

Professor **ARIEL HOURVITZ**

Director of IVF Unit

Shamir Medical Center, Tel-Aviv University, Israel

17:00 – 17:30 | *Coffee Break*

IV SESSION

Chairman: Professor **ARCHIL KHOMASURIDZE**

17:30 – 18:30

Moderator: Professor **NINO MUSERIDZE**

17:30 – 17:50 | How to Manage a World Class IVF Center" and "Obtaining Accreditation in
North America for IVF and Importation of Donor Gametes

Dr. **GRACE TAN**

Senior Administrator and compliance officer For Accreditation Canada
and Health Canada Inspections, OriginElle Clinics, Canada

17:50 – 18:10 | HPV Vaccination in Males: Has the Time Come?

Professor **ARCHIL CHKHOTUA**

Scientific Director, L. Managadze National Center of Urology

Secretary General, Georgian Urological Association, Georgia

18:10 – 18:30 | Adenomyosis – Problem in the Structure of Late Reproductive Age Infertility
 Professor **MAKA GEGECHKORI**
 Zurab Sabakhtarashvili Reproductive Clinic,
 Head of Science Department, Georgia

13:30 – 19:00 | *Discussion*
Book presentation

22/09/2024 Day 2 BALLROOM 1

09:00 – 10:00 | Registration

I SESSION Chairman: Professor **ARCHIL KHOMASURIDZE**
10:00 – 12:00 Moderator: Professor **NINO MUSERIDZE**

10:00 – 10:05 | Welcome addresses
 Professor **ARCHIL KHOMASURIDZE**
 President of Georgian Association of Reproductive Health, Georgia

 Professor **NINO MUSERIDZE**
 Medical Director of Georgian-German Reproductology Center, Georgia

10:05 – 10:30 | TMenopause Hormone Therapy as Primary Prevention of Diseases of Aging. DHEA and Testosterone Therapies to Correct Women's Hypo-Androgenism
 Professor **ANDREA GENAZZANI**
 President of International Academy of Human Reproduction, Italy

10:30 – 10:55 | Prostate Surgery and Ejaculation Spring Techniques
 Professor **GIAN MARIA BUSETTO**
 Associate Professor of Urology, University of Foggia, Italy

10:55 – 11:20 | Artificial Intelligence in Reproductive Medicine
 Professor **VYACHESLAV LOKSHIN**
 Academician of the National Academy of Sciences,
 Republic of Kazakhstan, President of the Kazakh Association of
 the Reproductive Medicine, Kazakhstan

11:20 – 11:45 | Preparation after Unsuccessful Programs
SHOLPAN KARIBAYEVA
 Candidate of Medical Sciences
 Director of Strategic Development, International Clinical Center for
 Reproductology PERSONA, Kazakhstan

11:45 – 12:00 | *Discussion*

12:00 – 12:30 | *Coffee Break*

II SESSION
12:30 – 14:30

Chairman: Professor **ARCHIL KHOMASURIDZE**
Moderator: Professor **NINO MUSERIDZE**

12:30 – 12:50 | Glycemic Control and Complication Rates in Pregnancy and Thirteen Years Post-Partum in Women With Microalbuminuria (Type 1 Diabetes, T1DM)

Professor **NATALIA ASATIANI**

Head, Dept. of Instrumental Diagnostics, National Center for Diabetes Research, Georgia

12:50 – 13:10 | Do Human Embryos Have the Ability of Self-Correction?

ADVA AIZER

Head of the IVF Laboratory Department of Obstetrics and Gynecology, The Sheba Medical Center, Israel

13:10 – 13:30 | Repeated Implantation Failure: how to Prepare a Patient for the Next Protocol

NATO SHAMUGIA

Associate Professor, Department of Obstetrics and Gynecology of RMANPO, Georgia

13:30 – 13:50 | Hormonal Contraception and Menopausal Hormone Therapy in the Condition of Haemostasis Disorders

Professor **ALEXANDER MAKATSARIA**

Academician of the Russian Academy of Sciences
Head of the Department of Obstetrics, Gynecology and Perinatal Medicine, Russia

13:50 – 14:10 | Aspirin For Prevention of Preeclampsia: For Whom, When and How Much?

MAMUKA NEMSADZE

Vice President of the Association of Obstetricians, Gynecologists and Perinatologists of Georgia

14:10 – 14:30 | PGTA Premium: Integrating Polyploidy Analysis, Quality Control and Carrier Screening for Optimal Reproductive Outcomes

Dr. **BERTHE YOUNESS**

Market Development Manager (EMEA), Reproductive Health Clinical Next-Generation Sequencing Division | Genetic Sciences Group
Reproduction genetics of Heidelberg University, Germany

14:30 – 16:30 | Lunch

III SESSION
16:30 – 18:30

Chairman: Professor **JENARO KRISTESASHVILI**
Moderator: Professor **NINO MUSERIDZE**

16:30 – 16:50 | Challenges in implementing an advanced minimally invasive surgery set up

RENE LAKY

Deputy Head Gynecology Division, Medical University of Graz, Austria

16:50 – 17:00 | Ultra Rapid Vitrification and Warming Protocol Confirming with Metabolic Fingerprinting Results

BIROL AYDIN

Head of Embryology Laboratory, Turkey (online)

17:10 – 17:30 | Oncofertility in BRCA1/2 Mutation Carrier Cancer Patients

ELENE MARIAMIDZE

Todua Clinic, Onco-Hematology Department, Georgia

17:30 – 17:50 | Personalized Controlled Ovarian Stimulation

ANA AIVAZOVA

Georgian-German Reproductology Center, Georgia

17:50 – 18:10 | Innovations in Oocyte Preservation Techniques

NIA NIZHARADZE

Georgian-German Reproductology Center, Georgia

18:10 – 18:30 | Congenital Ovarian Cysts and their Prenatal Diagnosis

NIKOLOZ SARAULI

Georgian-German Reproductology Center, Georgia

18:30 – 19:00 | Discussion

22/09/2024 Day 2 BALLROOM 2

09:30 – 10:00 | Registration

I SESSION

10:00 – 12:00

Chairman: Professor **TENGIZ ASATIANI**

Moderator: **NATO SHAMUGIA**

10:00 – 10:05 | Sustainable Development Goals in Georgia for Gynecology and Reproductive Medicine: Progress and Challenges

Professor **TENGIZ ASATIANI**

Chairman Association of Obstetricians and Gynecologists of Georgia, Georgia

10:05 – 10:30 | The Menopausal Transition: Hormonal Changes, Clinical Symptoms, Diagnosis, and Current Management Approaches

GEORGE TEVDORASHVILI

Associate Professor, Department of Obstetrics and Gynecology,
First University Clinic of Tbilisi State Medical University, Georgia

10:30 – 10:55 | Recurrent Implantation Failure- Reality or Fata Morgana?

Professor **IDO BEN AMI**

Head, IVF Unit, Shaare Zedak Medical Center, Israel

10:55 – 11:20 | Endometriosis and Infertility. Evidence-Based Management

Professor **GAMAL I. SEROUR**

AProf. of OB/GYN and Director International Islamic Center For Population
Studies and Research, Al Azhar University.

Clinical Director, The Egyptian

IVF&ET Center, Maadi, Egypt. FIGO Past President

11:20 – 11:45 | Failed IVF Protocol

TAMARA NADIRASHVILI

Georgian-German Reproductology Center, Georgia

11:45 – 12:00 | *Discussion*

12:00 – 12:30 | *Coffee Break*

II SESSION
12:30 – 14:30

Chairman: Professor **TENGIZ ASATIANI**
Moderator: Professor **NATO SHAMUGIA**

12:30 – 12:50 | Glycemic Control and Complication Rates in Pregnancy and Thirteen Years Postpartum in Women with Microalbuminuria (Type I Diabetes T1DM)

NIA METONIDZE

Georgian-German Reproductology Center, Georgia

12:50 – 13:10 | Periconception and Conception Genetic Testing-Problem Identification or Dilemma?

MAKA CHIPASHVILI

Clinical Geneticist, Associate Professor, Tbilisi State University, Georgia

13:10 – 13:30 | IN VITRO Patients Pregnancy Management, Thrombophilia, Preeclampsia

TEA KOLBAIA

Georgian-German Reproductology Center, Georgia

13:30 – 13:50 | IVM Opportunities, Realities and Perspectives in ART

MAKA OSEPAISHVILI

Clinic of Reproduction and Genetics “Next Generation” (online)

13:50 – 14:10 | Multiple Failed Embryo Transfer and PRP Therapy

OLIKO MURGHULIA

Georgian-German Reproductology Center, Georgia

14:10 – 14:30 | Artificial Intelligence for Sperm Selection

ALEXANDER KHELAIA

National Urology Centre, GGRC, Association of Urologists of Georgia

14:30 – 16:30 | *Lunch*

III SESSION
16:30 – 18:30

Chairman: Professor **TENGIZ ASATIANI**
Moderator: **Professor NATO SHAMUGIA**

16:30 – 16:50 | From InVitro to In Silico Concept in IVF Outcome Prediction with Neural Network

SERGEY SERGEYEV

Head, Embryolab – Georgian-German Reproduction Center, Georgia

16:50 – 17:10 | A Comprehensive KPI Assessment System in an IVF Laboratory

TAMAR DVALI

Georgian-German Reproductology Center, Georgia

17:10 – 17:30 | Hemorheological Changes During Physiological Pregnancy

Professor **MAKA MANTSKAVA**

Head of Rheology and Diagnostic Analytical Services Laboratory Ivane Beritashvili Experimental Center of Biomedicine, Georgia

17:30 – 17:50 | Dydrogesterone and Late Reproductive Age

Professor **TAMAR MAGULARIA**

Georgian-German Reproductology Center, Georgia

17:50 – 18:10 | IVF and Breast Cancer Risks

NINO CHIKOBAVA

Georgian-German Reproductology Center, Georgia

18:10 – 18:30 | Congenital Ovarian Cysts and their Prenatal Diagnosis

TAMTA MOTSONELIDZE

Georgian-German Reproductology Center, Georgia

18:30 – 19:00 | Discussion

5th International Conference “Infertility 35+”

21-22 September, 2024, Tbilisi, Georgia

Genetics; Fertility and Endometriosis

Scientific Program – Workshop

“Infertility 35 +” – Genetics; Fertility and Endometriosis

22/09/2024 Day 2 BALLROOM 3

09:30 – 10:00 | Registration

I SESSION

10:00 – 12:00

Chairman: Professor **NIKOLOZ KINTRAIA**

Moderator: Professor **VYACHESLAV LOKSHIN**

10:00 – 10:05 | Welcome addresses

Professor **NINO MUSERIDZE**

Medical Director, Georgian-German Reproductology Center, Georgia

10:05 – 10:20 | Pre-conceptional Carrier Screening

Professor **GOZDE YESIL SAYIN**

Istanbul University Medical Faculty

Lecturer in Medical Faculty, Rare Disease PhD, Genetic Counseling and Medical Genetics M.Sc. and PhD programs

Head of Whole Genome Based Newborn Screening Program,

SZAOmics, Acibadem University, Türkiye

10:20 – 10:40 | Preimplantation Genetic Testing for Aneuploidies and Single Gene Disorders

Professor **CUMHUR GOKHAN EKMEKCI**

Genetiks Genetic Disease Evaluation Center, Türkiye

10:40 – 11:00 | Importance of Pre-conceptional and Newborn Screening or Postnatal and Periconceptional Genetic Screening, Challenges and Utilities

Professor **GOZDE YESIL SAYIN**

Istanbul University Medical Faculty

Lecturer in Medical Faculty, Rare Disease PhD, Genetic Counseling and Medical Genetics M.Sc. and PhD programs

Head of Whole Genome Based Newborn Screening Program, SZAOmics,

Acibadem University, Türkiye

11:00 – 11:20 | A journey from IVF to unexpected ovarian cancer

Professor **ZAZA TSITSISHVILI**

MD. PhD, AHT Oncogynecologist, President of Georgian Society of Gynecological Oncology, Georgia

11:20 – 11:40 | Short-Fragment Nanopore Sequencing of Cell-Free DNA for Non-Invasive Prenatal Testing

Dr. **YARON GOIKHMAN**

Yale School of Public Health: MSc Global Health Management with emphasis on structuring and running large scale medical project in genetics, USA

11:40 – 12:00 | Non-Invasive Prenatal Testing (NIPT): Reliability, Challenges, and Future Directions

Professor **ANDREI KULLYEV**

Molecular Biology, Genetics, and Neurobiology/ Embryology, Micromanipulation, FISH (Fluorescence In Situ Hybridization), USA

12:00 – 12:30 | Coffee Break

II SESSION

12:30 – 13:20

Workshop “Infertility 35 +” – Endometriosis

Chairman: Professor **NIKOLOZ KINTRIAIA**

Moderator: Professor **VYACHESLAV LOKSHIN**

Moderator: Professor **EMMA VARTANYAN**

12:30 – 12:50 | Conservative Management of Endometriosis Prior to IVF Fertilization

Professor **EMMA VARTANYAN**

Department of Obstetrics and Gynecology of Pirogov Russian National Research Medical University, President of the self-regulating society Association of ART Clinics, Director of LLC “Test-Tube Babies” Clinic for Assisted Reproductive Technologies, obstetrician-gynecologist, reproductive specialist

III SESSION

12:50 – 14:30

Meeting of IFFS Associations of Georgia, Kazakhstan and Armenia

Chairman: Professor **NIKOLOZ KINTRIAIA**

Moderator: Professor **VYACHESLAV LOKSHIN**

Moderator: Professor **NINO MUSERIDZE**

12:50 – 13:10 | More Joy-It Is Time To See the Elephant in The Room?

Professor **EDGAR MOCANU**

President of the International Federation of Fertility Societies, Ireland

13:10 – 13:30 | Ethical and Moral Aspects of IVF

Professor **VYACHESLAV LOKSHIN**

Academician of the National Academy of Sciences, Republic of Kazakhstan, President of the Kazakh Association of the Reproductive Medicine, Kazakhstan

13:30 – 13:50 | History of ART in all of the world

Professor **VLADISLAV KORSACK**

General Director of ICRM, President of the Russian Association of Human Reproduction (RAHR), ESHREIM Community Council Member

13:50 – 14:10 | Reproductive Health in Armenia: Before and After the Revolution

Professor **EDUARD HAMBARTSOUMIAN**

President of the Association of Reproductive Medicine of Armenia

Head of the Department of Reproductive Medicine at the NIH of Armenia,
Director and founder of the Fertility Center clinic.

Member of the WHO Human Reproduction Program Policy and
Coordination Committee (PCC), Armenia

14:10 – 14:30 | Reproductology yesterday, today, tomorrow reality of Georgia

Professor **NINO MUSERIDZE**

Head of the Oncofertility Association of Georgia

Founder and Medical Director,

Georgian-German Reproductology Center, Georgia

14:10 – 14:30 | Lunch

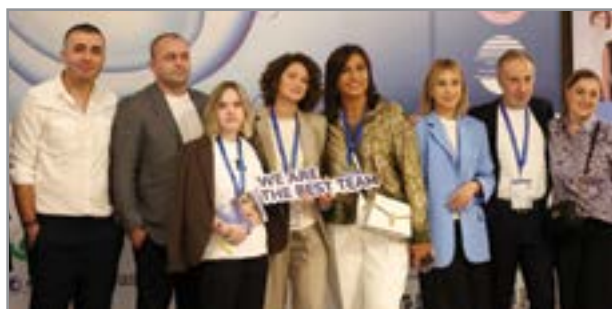












SYMPOSIUM AND WORKSHOP OF THE 20TH WORLD CONGRESS ON HUMAN REPRODUCTION: "INFERTILITY 35+"

GEORGIAN-GERMAN REPRODUCTION CENTER
GAO-GEORGIAN ASSOCIATION OF ONCOFERTILITY

TBILISI, GEORGIA, 2025

INFERTILITY 35+

WORKSHOP



The International Academy
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Georgian Association of
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