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7th International Scientific Conference & Workshop “Infertility 35+”



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Genome-Wide Preimplantation Genetic Testing
for Monogenic Disorders in Real Clinical Practice

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Beyond Conventional PGT: Integrating
Polygenic Risk Analysis into PGT-A and PGT-M:
A Systematic Review of Clinical Utility, Technical
Challenges, and Ethical Considerations

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Contraception in Women Aged 35+

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Fast & Furious: Exploring the Orbit
of Fast Vitrification and Warming in Human IVF

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Blastocyst Development and Embryo Ploidy in Women with
Genotype-Confirmed HPV-Associated CIN1:
A Retrospective Cohort Study

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MEDICAL TIMES

7th International Scientific Conference & Workshop

№5

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ON BEHALF OF THE GEORGIAN ASSOCIATION OF ONCOFERTILITY AND THE GEORGIAN-GERMAN REPRODUCTIVE MEDICINE CENTER

On September 12–13, 2026, the **7th International Scientific Conference-Workshop “Infertility 35+”** will be held in Tbilisi, Georgia, at the **Sheraton Grand Tbilisi Metechi Palace**. The conference is organized by the **Georgian Association of Oncofertility**, with the support of the **Georgian-German Reproductive Medicine Center** and the Georgian Associations of Urologists, Obstetricians and Gynecologists, Endocrinologists, and Reproductive Medicine Specialists.

The conference is being held for the seventh consecutive year and continues to grow in international scope and significance. This year, leading physicians, scientists, and experts from the **United States, Canada, Italy, Germany, Israel, Egypt, Austria, Kazakhstan, Turkey, Armenia, Azerbaijan**, and, of course, **Georgia**, will participate in the event.

Alongside international experts, scientific presentations will also be delivered by Georgian physicians, as well as residents in Obstetrics and Gynecology and Reproductive Medicine. I consider this an important opportunity for young specialists to advance their professional knowledge, exchange experience, and become more actively integrated into the international scientific community.

The scientific program covers the fields of **Reproductive Medicine, Obstetrics and Gynecology, Urology, Clinical Oncology, Endocrinology, and Oncological Surgery**. Participants will have the opportunity to learn about modern approaches, the latest scientific research, innovative technologies, and evidence-based practices in each of these fields.

I would particularly like to emphasize that participants who register in advance will receive certificates of participation and will be awarded **12 Continuing Professional Development (CPD/CME) credit points**.

An important scientific component of the conference is our collaboration with the medical journal **“Medical Times.”** Scientific articles and abstracts submitted by conference speakers will be published in a special issue of the journal.

“Medical Times” is a peer-reviewed medical journal dedicated to the dissemination of current research, scientific developments, and clinical experience in the field of reproductive medicine. Our goal is to provide Georgian and international researchers and medical professionals with an appropriate platform for presenting and disseminating their scientific work within the international scientific community.

As part of the conference, the electronic edition of the journal will be published for the **third consecutive year**. The electronic edition will be hosted on a dedicated platform based on **OJS (Open Journal Systems)**.

Scientific publications will be assigned a **Digital Object Identifier (DOI)**, which will contribute to increasing their visibility, accessibility, and dissemination within the international scientific community.

It is particularly important to me that we have been able to offer Georgian physicians and researchers the opportunity to publish their scientific articles in the **electronic journal completely free of charge**. In addition, registration for Georgian physicians to attend the conference is offered free of charge every year.

As a special gift, each conference participant will receive a new issue of **“Medical Times”**, as well as a new medical textbook authored by me.

Due to the particularly strong interest in the conference, approximately **400 physicians have already registered**, including international specialists who will travel to Georgia specifically to attend this international scientific event.

The conference will take place over two days, with the scientific program running simultaneously in **four different halls**. One of the halls will be dedicated to practical workshops, which will be conducted by leading specialists from **Turkey, the United States, and Japan**.

During the workshops, participants will have the opportunity to learn about modern techniques and practical approaches, discuss interesting and challenging clinical cases, and participate in practical seminars alongside the theoretical sessions. I believe that this format is particularly important for translating scientific knowledge into clinical practice and further developing professional skills.

It is especially significant to us that representatives of various internationally recognized, world-leading professional and scientific associations will attend the conference. Their participation once again highlights the international significance of the event and creates an important opportunity for the **Georgian Association of Oncofertility** to strengthen cooperation with leading international professional organizations and pursue membership in such organizations.

We believe that organizing international scientific events of this scale contributes to the development of medical science and clinical practice in Georgia, promotes the integration of Georgian physicians into the international scientific community, facilitates the exchange of professional experience, and supports the broader implementation of modern, evidence-based medical approaches.

Finally, on behalf of the **Georgian Association of Oncofertility** and the **Georgian-German Reproductive Medicine Center**, I would like to express our sincere gratitude to the supporter of the conference, the **Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs of Georgia**, for its valuable support and cooperation.

Respectfully,

Professor NINO MUSERIDZE

Clinical Director, Georgian-German Reproductive Medicine Center (GGRC)

President, Georgian Association of Oncofertility

Editor-in-Chief, **“Medical Times”**

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საქართველოს ონკოფერტილობის ასოციაციისა და ქართულ-გერმანული რეპროდუქციული მედიცინის ცენტრის სახელით

2026 წლის 12–13 სექტემბერს, ქ. თბილისში, სასტუმრო „მერატონ გრანდ თბილისი მეტეხი პალასში“, საქართველოს ონკოფერტილობის ასოციაციის ორგანიზებით, ქართულ-გერმანული რეპროდუქციული მედიცინის ცენტრის, საქართველოს უროლოგთა, მეან-გინეკოლოგთა, ენდოკრინოლოგთა და რეპროდუქტოლოგთა ასოციაციების მხარდაჭერით, გაიმართება მეშვიდე საერთაშორისო სამეცნიერო კონფერენცია-ვორქშოპი „**უნაყოფობა 35+**“.

კონფერენცია უკვე მეშვიდედ ტარდება და ყოველწლიურად სულ უფრო ფართო საერთაშორისო მასშტაბს იძენს. წელს ღონისძიებაში მონაწილეობას მიიღებენ მსოფლიოს სხვადასხვა ქვეყნის წამყვანი ექიმები, მეცნიერები და დარგის ექსპერტები აშშ-დან, კანადიდან, იტალიიდან, გერმანიიდან, ისრაელიდან, ეგვიპტიდან, ავსტრიიდან, ყაზახეთიდან, თურქეთიდან, სომხეთიდან, აზერბაიჯანიდან და, რა თქმა უნდა, საქართველოდან.

საერთაშორისო ექსპერტებთან ერთად, სამეცნიერო მოხსენებებს წარადგენენ ქართველი ექიმები და ასევე მეან-გინეკოლოგიისა და რეპროდუქტოლოგიის რეზიდენტები. ეს ახალგაზრდა სპეციალისტებისთვის პროფესიული განვითარების, გამოცდილების გაზიარებისა და საერთაშორისო სამეცნიერო სივრცეში ინტეგრაციის მნიშვნელოვან შესაძლებლობას წარმოადგენს.

კონფერენციის სამეცნიერო პროგრამა მოიცავს რეპროდუქტოლოგიის, მეან-გინეკოლოგიის, უროლოგიის, კლინიკური ონკოლოგიის, ენდოკრინოლოგიისა და ონკოქირურგიის მიმართულებებს. მონაწილეები გაეცნობიან თითოეულ სფეროში არსებულ თანამედროვე მიდგომებს, უახლეს სამეცნიერო კვლევებს, ინოვაციურ ტექნოლოგიებსა და მტკიცებულებებზე დაფუძნებულ პრაქტიკას.

განსაკუთრებით მნიშვნელოვანია, რომ კონფერენციაზე წინასწარ რეგისტრირებულ მონაწილეებს გადაეცემათ მონაწილეობის სერტიფიკატები და მიენიჭებათ **უწყვეტი პროფესიული განათლების (უპგ) 12 კრედიტ-ქულა**.

კონფერენციის მნიშვნელოვანი სამეცნიერო კომპონენტია თანამშრომლობა სამედიცინო ჟურნალ „**Medical Times**“-თან. მომხსენებელთა სამეცნიერო სტატიები და აბსტრაქტები გამოქვეყნდება ჟურნალის სპეციალურ გამოცემაში.

„**Medical Times**“ არის რეცენზირებული სამედიცინო ჟურნალი, რომელიც განსაკუთრებულ ყურადღებას უთმობს რეპროდუქციული მედიცინის სფეროში თანამედროვე კვლევების, სამეცნიერო სიახლეებისა და კლინიკური გამოცდილების გავრცელებას. ჩვენი მიზანია ქართველი და უცხოელი მკვლევრებისა და სამედიცინო პროფესიონალების სამეცნიერო ნაშრომებისთვის საერთაშორისო სამეცნიერო სივრცეში სათანადო პლატფორმის შექმნა.

კონფერენციის ფარგლებში ჟურნალის ელექტრონული ვერსია წელს უკვე მესამედ გამოიცემა. ელექტრონული გამოცემა განთავსდება OJS-ის (Open Journal Systems) სისტემაზე დაფუძნებულ სპეციალურ პლატფორმაზე. სამეცნიერო პუბლიკაციებს მიენიჭება **ციფრული ობიექტის იდენტიფიკატორი (DOI)**, რაც ხელს შეუწყობს მათი საერთაშორისო სამეცნიერო სივრცეში ხილვადობის, ხელმისაწვდომობისა და გავრცელების გაზრდას.

ჩვენთვის განსაკუთრებით მნიშვნელოვანია ის შესაძლებლობა, რომელიც ქართველ ექიმებსა და მკვლევრებს ეძლევათ – **ელექტრონულ ჟურნალში სამეცნიერო სტატიის გამოქვეყნება მათთვის სრულიად უსასყიდლოდ არის შესაძლებელი**. ასევე, ყოველწლიურად ქართველი ექიმებისთვის კონფერენციაზე რეგისტრაცია უფასოა.

კონფერენციის თითოეულ მონაწილეს საჩუქრად გადაეცემა ჟურნალ „Medical Times“-ის ახალი გამოცემა, ასევე ჩემი ავტორობით მომზადებული ახალი სახელმძღვანელო.

კონფერენციისადმი განსაკუთრებული ინტერესიდან გამომდინარე, ღონისძიებაზე უკვე რეგისტრირებულია **400-მდე ექიმი**, მათ შორის უცხოელი სპეციალისტები, რომლებიც სპეციალურად ესტუმრებიან საქართველოს საერთაშორისო სამეცნიერო ღონისძიებაში მონაწილეობის მისაღებად.

კონფერენცია ორი დღის განმავლობაში გაგრძელდება და სამეცნიერო პროგრამა ოთხ სხვადასხვა დარბაზში პარალელურ რეჟიმში განხორციელდება. ცალკე დარბაზი დაეთმობა პრაქტიკულ ვორქშოპებს, რომლებსაც თურქეთის, აშშ-ისა და იაპონიის წამყვანი სპეციალისტები ჩაატარებენ.

ვორქშოპების ფარგლებში მონაწილეებს შესაძლებლობა ექნებათ გაეცნონ თანამედროვე მეთოდებსა და პრაქტიკულ მიდგომებს, განიხილონ საინტერესო და რთული კლინიკური შემთხვევები და თეორიულ სწავლებასთან ერთად მონაწილეობა მიიღონ პრაქტიკულ სემინარებში. აღნიშნული ფორმატი განსაკუთრებით მნიშვნელოვანია ცოდნის პრაქტიკაში გამოყენებისა და პროფესიული უნარების გაღრმავებისთვის.

ჩვენთვის განსაკუთრებული მნიშვნელობის მატარებელია ის ფაქტიც, რომ კონფერენციას დაესწრებიან სხვადასხვა საერთაშორისო, მსოფლიო მნიშვნელობის პროფესიული და სამეცნიერო ასოციაციების წარმომადგენლები. მათი მონაწილეობა კიდევ ერთხელ უსვამს ხაზს ღონისძიების საერთაშორისო მნიშვნელობას და ქმნის მნიშვნელოვან შესაძლებლობას საქართველოს ონკოფერტილობის ასოციაციის საერთაშორისო პროფესიულ ორგანიზაციებთან თანამშრომლობისა და გაწევრიანების მიმართულებით.

მიგვაჩნია, რომ ასეთი მასშტაბის საერთაშორისო სამეცნიერო ღონისძიებების ჩატარება ხელს შეწყობს საქართველოში სამედიცინო მეცნიერებისა და კლინიკური პრაქტიკის განვითარებას, ქართველი ექიმების საერთაშორისო სამეცნიერო სივრცეში ინტეგრაციას, პროფესიული გამოცდილების გაზიარებას და თანამედროვე, მტკიცებულებებზე დაფუძნებული სამედიცინო მიდგომების კიდევ უფრო ფართოდ დანერგვას.

დასასრულს, საქართველოს ონკოფერტილობის ასოციაციისა და ქართულ-გერმანული რეპროდუქციული მედიცინის ცენტრის სახელით, განსაკუთრებულ მადლობას ვუხდით კონფერენციის მხარდამჭერს – **საქართველოს ოკუპირებული ტერიტორიებიდან დევნილთა, შრომის, ჯანმრთელობისა და სოციალური დაცვის სამინისტროს** – მხარდაჭერისა და თანამშრომლობისთვის.

პატივისცემით,

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ABSTRACT BOOK

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BIOTECHNOLOGICAL SOLUTIONS FOR PREVENTING MISMATCHES AND ENHANCING SAFETY IN IVF AND PGT APPLICATIONS

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ABSTRACT

Background: Modern IVF laboratories involve complex, operator-dependent workflows in which manual handling, repetitive sample transfers, and fragmented monitoring systems create ongoing risks of sample mismatch, contamination, and procedural variability. While embryology laboratories have rapidly adopted advanced culture systems and imaging technologies, critical aspects such as traceability, biopsy verification, contamination monitoring, and KPI-driven quality control remain insufficiently standardized across routine practice. This presentation introduces a genetics-oriented framework for IVF laboratory monitoring and safety by integrating molecular traceability principles into embryology workflows.

Methods: The presented approach combines electronic witnessing systems, barcode-based embryo tracking, AI-supported monitoring tools, SNP-based genomic verification strategies, and standardized laboratory KPIs to improve procedural reproducibility and reduce human-dependent variability throughout IVF applications, from oocyte retrieval to embryo transfer and cryopreservation.

Results: Several emerging technologies and workflow models are presented, including wireless witnessing systems for preventing gamete and embryo mismatches, smart biopsy monitoring platforms with real-time operator guidance and retrospective audit capabilities, incubator-compatible imaging systems for standardized embryo assessment, and high-capacity cryostorage solutions designed to optimize sample logistics and traceability. In parallel, the presentation highlights how genomic SNP information generated during modern PGT applications can provide an additional biological safety layer beyond conventional morphology-based IVF workflows. These approaches enable confirmation of embryo-parent consistency, detection of maternal or external contamination, identification of sample mix-up events, and recognition of polyploidy-related abnormalities that may not be adequately resolved by traditional copy-number-based PGT-A approaches alone. The presentation also discusses the evolution of PGT technologies from conventional PGT-A toward integrated SNP-supported genomic embryo assessment models. Particular emphasis is placed on the role of SNP haplo-

typing and kinship analysis in improving confidence during embryo selection, donor-related IVF workflows, biopsy handling, and multi-site laboratory operations. Real-world validation examples and multicenter monitoring strategies are presented to demonstrate how genomic traceability can complement electronic witnessing systems in IVF laboratories.

Conclusions: By transferring the precision, auditability, and traceability standards routinely applied in molecular genetics laboratories into IVF practice, this approach proposes a next-generation IVF safety model in which laboratory processes become digitally monitored, biologically verifiable, and retrospectively auditable. The integration of genomic verification tools with embryology workflows may contribute to safer IVF applications, improved reproducibility between laboratories, and more standardized embryo handling procedures in modern reproductive medicine.

Keywords: contamination detection; electronic witnessing; embryo verification; molecular traceability; SNP haplotyping.

Declarations

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EFFECTIVENESS OF RAPID WARMING PROTOCOLS FOR VITRIFIED BLASTOCYSTS

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ABSTRACT

Background: Embryo warming is a critical step in vitrified blastocyst transfer cycles, with the potential to influence both embryological and clinical outcomes. In 2024, the Georgian-German Reproduction Center (GGRC) IVF Clinic implemented a rapid warming protocol, replacing the conventional multi-step warming method. This study evaluated the effectiveness of the rapid warming protocol by comparing laboratory and clinical outcomes before and after its implementation.

Methods: This retrospective cohort study included all vitrified-warmed blastocyst transfer cycles performed at the GGRC IVF Clinic over two consecutive two-year periods. Cycles performed during the two years following implementation of the rapid warming protocol were compared with those performed during the preceding two years, during which the conventional warming protocol was routinely used. The primary outcomes included the number of warmed blastocysts, post-warming survival rate, blastocyst re-expansion rate, and implantation rate.

Results: A total of 9,402 vitrified-warmed blastocysts were included in the analysis, comprising 4,275 blastocysts in the conventional warming group and 5,127 blastocysts in the rapid warming group. The post-warming survival rate was 95% in the conventional warming group and 99% in the rapid warming group. Blastocyst re-expansion rates were 50% and 71%, respectively. Implantation rates were 48% in the conventional warming group and 54% in the rapid warming group.

Conclusions: The rapid warming protocol demonstrated excellent post-warming survival and favorable embryological and clinical outcomes, with numerically higher rates of survival, blastocyst re-expansion, and implantation than the conventional warming protocol. In addition, the rapid warming method reduced the time required to warm embryos, making it a more efficient and practical approach for routine clinical use, particularly in high-volume IVF clinics where improved workflow efficiency and time savings are important.

Keywords: blastocyst; embryo warming; implantation; in vitro fertilization; rapid warming; vitrification.

Declarations

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FAST & FURIOUS: EXPLORING THE ORBIT OF FAST VITRIFICATION AND WARMING IN HUMAN IVF

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ABSTRACT

Background: A stepwise removal of Cryoprotectants at rehydration is a fundamental principle in

cryobiology. The theory behind this approach is to minimize damage to the blastocyst. Blastocyst and oocyte vitrification/warming protocols are time-consuming and labor-intensive. Therefore, the purpose of this study was to determine if embryos warmed using a one-step rehydration protocol with a more efficient workflow resulted in comparable pregnancy rates to the standard multi-step rehydration protocol.

Methods: Vitrification of blastocysts was undertaken after a two-step loading with cryoprotectant agents (Irvine Scientific; Santa Ana, CA) at 24°C. Assisted collapsing was done prior to vitrification by putting the blastocyst on an inverted microscope equipped with a laser system (Lykos, Hamilton Thorne) and one shot (100% power, 500µs pulse length) was applied. Then, blastocysts were placed in an equilibration solution containing 7.5% (v/v) ethylene glycol (EG) and 7.5% (v/v) dimethyl sulfoxide (DMSO). After 4 minutes, the blastocysts were washed quickly in vitrification solution, which is the base medium containing 15% (v/v) DMSO, 15% (v/v) EG and 0.5M sucrose for 1 minute and transferred onto the HSV using a Polycarbonate micropipette (Origio, Denmark). Immediately after the loading of one blastocyst in a 1 µL drop on the HSV, the straws were heat sealed, then plunged into liquid nitrogen (LN2), and secondarily stored inside 5 mL LN2 prefilled goblets. Timeline for vitrifying blastocysts requires a total of 5 minutes. **Multi-Step Rehydration** To remove the cryoprotectants, blastocysts were warmed and cryoprotectants diluted in a three-step process. With the HSV submerged in LN2, the inner straw was removed, and then the carrier with the blastocysts was removed from the LN2 and placed directly into a pre-warmed (37°C) 400µL drop of thawing solution (TS) containing 1.0M sucrose for one minute. The blastocysts were then transferred into a fresh 50µL drop of 1M sucrose and immediately connected with a fresh 50 µL drop of dilution solution (DS) containing 0.5M sucrose. After 3 minutes, they were then connected with another 50 µL drop of 0.5M sucrose for 2 minutes. Then blastocysts were transferred to a 50 µL drop of 0.5M sucrose solution and connected with a 50 µL drop of wash solution for 3 minutes. Then the blastocysts were connected to another 50 µL drop of wash solution for an additional 2 minutes. Thereafter, the blastocysts were transferred through the 2x50 µL of wash solution and returned into the transfer dish containing the culture medium (SAGE Blastocyst Medium, Trumbull, CT, USA) with additional 20% protein until transfer. The timeline for standard warming of blastocysts requires a total of 11 minutes.

One-Step Rehydration The 1M sucrose solution was kept overnight in an incubator set at 37°C. Before the warming of blastocysts, a 400µL drop of this pre-warmed 1.0M sucrose was placed into a dish on a heating stage set at 38°C to assure 37°C.

This was a retrospective cohort study of a total of 5017 vitrified/warmed embryo transfers (FET). The study data includes a retrospective review of clinical outcomes of 2411 FETs using a one-step rehydration protocol. This data set was then compared to results from the control group obtained from 2606 FETs where the standard multi-step rehydration protocol was used. The primary outcome was the live birth rate. The secondary outcomes were survival, positive pregnancy, clinical pregnancy, implantation, and ongoing pregnancy rate.

Results: Survival rates were identical between the two groups (99.5%). The clinical pregnancy

rate was 61.3% in the one-step warming protocol, which was comparable to 59.9% in the multi-step rehydration protocol. There was no significant increase in the ongoing pregnancy rate with 51.4% in the one-step rehydration vs 50.1% in the multi-step rehydration group as well as the implantation rate with 60.0% vs 57.0%. The live birth rate between single vs multi was 51.3% vs 48.5%, respectively. Moreover, there was no difference in gestational age between one-step vs multi-step (37.6 ± 2.4 vs 37.6 ± 2.1). There was no significant difference in birth weight between single vs multi-step (3267 ± 672 g vs 3253 ± 609 g).

Conclusions: A one-step rehydration protocol allowing faster rehydration resulted in consistent

high survival rates of blastocysts. Furthermore, the 1-minute one-step rehydration protocol showed similar positive pregnancy and clinical pregnancy rates with similar implantation and ongoing pregnancy rates when compared to the 11 minutes multi-step rehydration protocol. The protocol presented here makes laboratory techniques for warming blastocysts simpler and therefore contributes to a meaningful optimization of laboratory resources. It reduces the unnecessary time blastocysts are exposed to room temperature and in turn reduces stress to the blastocysts. The protocol is safe, reliable and significantly improves laboratory efficiency. It allows for more embryos transfers daily without creating additional stress nor compromises safety. As a more efficient procedure it contributes to increased productivity by supporting flexibility & optimized workflow (reducing labor to 95%, and cost by 40%). Embryology Team feeling of improved quality of life at work (increased staff satisfaction, which contributes to patient satisfaction). Simplification from a multi-step to a single-step procedure minimizes repetitive tasks. It's easier to learn to achieve proficiency faster. With the continued rise in the number of ART cycles and shortage of proficient and competent staff, this protocol is truly impactful by expanding existing laboratory capacities and reducing workload pressure.

Keywords: short dehydration, short rehydration, one-step warming, blastocysts, vitrification, warming.

Declarations

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EMBRYO CULTURE TO THE BLASTOCYST STAGE AND ARTIFICIAL INTELLIGENCE TO FACILITATE SINGLE EMBRYO TRANSFER IN ASSISTED REPRODUCTIVE TECHNOLOGY

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ABSTRACT

Background: Single blastocyst transfer has become one of the most important strategies in assisted reproductive technology (ART) and represents a major achievement in modern embryology laboratories. The principal advantage of this approach is the significant reduction in multiple pregnancies, which are associated with increased risks for both the mother and the newborn, including preterm birth, low birth weight, and obstetric and neonatal complications. By transferring a single embryo at the blastocyst stage, fertility clinics can maintain high pregnancy rates while improving maternal and neonatal safety. Consequently, elective single blastocyst transfer (eSBT) is now widely recommended as a safe and effective strategy in contemporary ART. This review summarizes current principles of blastocyst culture and highlights the emerging role of artificial intelligence in embryo assessment and selection.

Methods: Current evidence regarding embryo culture systems, blastocyst development, and embryo selection was reviewed. Particular emphasis was placed on laboratory conditions required to support optimal embryo development, including pH, temperature, osmolality, humidity, and oxygen concentration. Recent advances in artificial intelligence and machine-learning technologies for embryo assessment were also examined, with particular focus on the iDAScore system developed by the Vitrolife Group. The review discusses the integration of time-lapse imaging, AI-assisted embryo evaluation, and their potential role in improving embryo selection while reducing inter-observer variability among embryologists.

Conclusions: Optimized embryo culture systems remain fundamental for successful blastocyst development and the implementation of elective single blastocyst transfer. Artificial intelligence represents an important advancement in embryo assessment by providing standardized, objective support for embryo selection. The integration of AI-based technologies such as iDAScore into modern embryology laboratories may contribute to improved embryo selection, enhanced laboratory consistency, and continued advances in the safety and effectiveness of assisted reproductive technology.

Keywords: artificial intelligence; blastocyst culture; embryo culture; elective single blastocyst transfer; iDAScore; pregnancy outcomes.

Declarations

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INTEGRATED MANAGEMENT STRATEGIES FOR HEMODIALYSIS VASCULAR ACCESS PRESERVATION AND LONG-TERM OUTCOMES

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ABSTRACT

Background: Reliable vascular access remains the cornerstone of successful hemodialysis, directly influencing treatment adequacy, patient survival, and quality of life. Despite advances in dialysis technology, vascular access dysfunction continues to be a major cause of morbidity, hospitalization, and increased healthcare costs. An integrated multidisciplinary strategy combining surgical, endovascular, and catheter-based approaches is essential for maintaining long-term vascular access and improving patient outcomes. This review evaluates the effectiveness of an integrated dialysis access management model incorporating long-term tunneled central venous catheters, endovascular interventions, and arteriovenous (AV) fistula preservation surgery in optimizing vascular access patency and reducing complications.

Methods: This review summarizes current clinical practices and evidence regarding the management of hemodialysis vascular access. The integrated approach includes individualized patient assessment, timely placement of tunneled dialysis catheters when permanent access is unavailable, regular surveillance of AV fistulas, and minimally invasive endovascular procedures such as balloon angioplasty and thrombectomy for stenotic or thrombosed access. Surgical revision and reconstruction are considered when endovascular treatment alone is insufficient. Multidisciplinary decision-making guides the selection of appropriate interventions based on patient characteristics, vascular anatomy, and clinical conditions.

Results: Early detection and timely treatment of vascular access dysfunction significantly improve primary and secondary patency rates while reducing dependence on temporary catheter access. Endovascular interventions effectively restore access function in many patients, delaying or avoiding the need for new access creation. Surgical preservation procedures remain essential for complex vascular lesions, recurrent stenosis, and cases unsuitable for endovascular correction. Long-term tunneled catheters provide safe and effective access for patients awaiting AV fistula maturation or those without options for permanent access. The coordinated appli-

cation of these strategies contributes to reduced access-related infections, fewer hospitalizations, and improved continuity of dialysis therapy.

Conclusions: Integrated management of dialysis vascular access, combining long-term catheter utilization, advanced endovascular techniques, and AV fistula preservation surgery, represents an effective approach for maximizing access longevity and improving clinical outcomes. Close collaboration among nephrologists, vascular surgeons, interventional specialists, and dialysis teams is fundamental to achieving optimal long-term vascular access management.

Keywords: arteriovenous fistula; AV fistula preservation; balloon angioplasty; endovascular intervention; hemodialysis; long-term catheter; thrombectomy; tunneled dialysis catheter; vascular access; vascular surgery.

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BLOOD HEMORHEOLOGY AND ITS ROLE IN THE DEVELOPMENT AND MANAGEMENT OF PATHOPHYSIOLOGICAL PROCESSES: AN OBSTETRIC AND GYNECOLOGICAL PERSPECTIVE

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ABSTRACT

Background: Blood hemorheology, which encompasses the flow properties of blood, including plasma viscosity, whole blood viscosity, erythrocyte deformability, and erythrocyte aggregation, plays a fundamental role in maintaining adequate tissue perfusion and oxygen delivery. Alterations in hemorheological parameters contribute to microcirculatory dysfunction, endothelial injury, inflammation, and thrombosis, thereby influencing the pathogenesis of numerous diseases. In obstetrics and gynecology, physiological and pathological changes in blood rheology have important implications for maternal and fetal outcomes. This narrative review examines the role of blood hemorheology in the development of pathophysiological processes in obstetrics and gynecology and discusses its clinical significance for disease prevention, diagnosis, and management.

Methods: A narrative review of the current scientific literature was conducted, focusing on the relationship between hemorheological alterations and common obstetric and gynecological disorders. Particular attention was given to pregnancy-associated physiological changes, hypertensive disorders of pregnancy, placental insufficiency, recurrent pregnancy loss, thromboembolic complications, and gynecological conditions associated with impaired microcirculation.

Results: Pregnancy is characterized by adaptive changes in blood viscosity and coagulation that support placental circulation while increasing thrombotic risk. Pathological disturbances in hemorheology contribute to endothelial dysfunction, impaired uteroplacental perfusion, placental ischemia, and adverse pregnancy outcomes, including preeclampsia, fetal growth restriction, recurrent miscarriage, and preterm birth. In gynecological practice, altered blood rheology has been associated with chronic inflammatory disorders, endometriosis, pelvic venous disease, and postoperative thromboembolic events. Early identification of hemorheological abnormalities, together with individualized preventive and therapeutic strategies-including anticoagulant therapy when indicated, optimization of cardiovascular risk factors, and

improvement of microcirculation-may reduce maternal morbidity and improve reproductive outcomes.

Conclusions: Blood hemorheology represents an important but often underrecognized component of the pathophysiology of obstetric and gynecological disorders. Integrating hemorheological assessment into clinical practice may facilitate earlier diagnosis, more personalized treatment, and improved maternal and reproductive health outcomes. Further clinical studies are warranted to define standardized diagnostic markers and evidence-based therapeutic approaches.

Keywords: blood hemorheology; blood viscosity; endothelial dysfunction; erythrocyte deformability; microcirculation; obstetrics and gynecology; placental insufficiency; pregnancy; pre-eclampsia; recurrent pregnancy loss.

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FERTILITY AND EXPERIMENTAL RHEOLOGICAL STUDIES

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ABSTRACT

Background: Fertility is a complex biological process that depends on coordinated interactions among the reproductive system, endocrine regulation, vascular function, and tissue microcirculation. Recent experimental studies have highlighted the importance of blood hemorheological properties, including viscosity, erythrocyte deformability, platelet activity, and microcirculatory regulation, in maintaining reproductive function and supporting successful implantation and pregnancy. This review analyzes the role of experimental rheological studies in understanding fertility-related processes and evaluates the potential significance of hemorheological parameters in reproductive medicine.

Methods: A review of experimental and clinical research data was conducted, focusing on the relationship between blood rheological characteristics and reproductive function. Studies investigating microcirculation, endothelial function, ovarian and endometrial blood supply, the gamete environment, implantation processes, and pregnancy-associated vascular adaptation were analyzed.

Results: Experimental investigations demonstrate that impaired rheological properties may adversely affect tissue oxygenation, vascular resistance, and perfusion of reproductive organs. Alterations in blood viscosity, erythrocyte deformability, and microvascular circulation have been associated with disturbances in endometrial receptivity, implantation failure, and adverse reproductive outcomes. Experimental models suggest that optimizing rheological parameters may improve microcirculatory conditions and offer new perspectives on fertility preservation and assisted reproductive technologies. Assessment of rheological markers may become a valuable complementary tool for identifying patients with increased reproductive risk and for developing personalized therapeutic approaches.

Conclusions: Experimental rheological research provides important insights into the vascular and microcirculatory mechanisms underlying fertility. Understanding the interaction between blood rheology and reproductive function may contribute to the development of innovative

diagnostic and therapeutic strategies in reproductive medicine. Further experimental and clinical studies are required to establish the predictive value of rheological biomarkers and their practical application in fertility management.

Keywords: assisted reproductive technologies; blood viscosity; endometrial receptivity; erythrocyte deformability; experimental studies; fertility; hemorheology; implantation; microcirculation; reproductive medicine.

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ABNORMAL PLACENTAL ADHERENCE AND THE IMPORTANCE OF ITS PRENATAL DIAGNOSIS

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ABSTRACT

Background: Abnormal placental adherence encompasses placenta accreta spectrum (PAS) disorders, including placenta accreta, increta, and percreta, as well as placenta previa when associated with abnormal placental invasion. The incidence of these conditions has increased owing to rising rates of cesarean delivery, advanced maternal age, and the use of assisted reproductive technologies (ART). Placenta accreta is characterized by abnormal adherence of the placenta to the uterine wall, preventing normal placental separation after delivery and increasing the risk of severe obstetric hemorrhage. In placenta increta, the placental villi invade the myometrium, whereas in placenta percreta, invasion extends through the uterine wall and may involve adjacent organs, such as the bladder or bowel. Prenatal diagnosis and appropriate multidisciplinary management are essential for reducing maternal morbidity and mortality.

Methods: Three surrogate mothers with a history of previous cesarean delivery were evaluated at the Georgian-German Reproductive Center. Ultrasonographic examination identified different forms of abnormal placental adherence. Magnetic resonance imaging (MRI) was subsequently performed to assess the extent of placental invasion and involvement of adjacent pelvic organs. Based on the imaging findings, all three patients underwent planned cesarean delivery with multidisciplinary surgical management.

Results: Abnormal placental adherence was confirmed in all three cases. Placenta percreta represented the greatest surgical challenge because of placental invasion into adjacent pelvic organs. In such cases, successful management required the involvement of a multidisciplinary team, including obstetricians, general surgeons, and urologists. Prenatal diagnosis facilitated appropriate surgical planning and preparation for potential massive obstetric hemorrhage.

Conclusions: Early antenatal diagnosis using ultrasonography and magnetic resonance imaging plays a pivotal role in the management of placenta accreta spectrum disorders. Accurate prenatal identification allows appropriate delivery planning, multidisciplinary team involvement, and timely surgical intervention, thereby reducing maternal morbidity and mortality associated with severe obstetric hemorrhage.

Keywords: assisted reproductive technology; magnetic resonance imaging; placenta accreta spectrum; placenta increta; placenta percreta; placenta previa; pregnancy; prenatal diagnosis; ultrasonography.

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EVIDENCE-BASED EVALUATION OF IVF ADD-ONS: ARE WE IMPROVING OUTCOMES OR EXPANDING HOPE?

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ABSTRACT

Background: In vitro fertilization (IVF) has evolved rapidly over the last two decades, accompanied by the increasing use of various adjunctive interventions, commonly referred to as “IVF add-ons.” These include endometrial scratching, platelet-rich plasma (PRP), time-lapse imaging, assisted hatching, immunological therapies, embryo glue, preimplantation genetic testing for aneuploidy (PGT-A), endometrial receptivity analysis (ERA), growth hormone supplementation, and others. While many of these interventions are widely offered in clinical practice, their true effectiveness and evidence base remain controversial. This review critically evaluates the current evidence regarding commonly used IVF add-ons. It assesses whether these interventions significantly improve reproductive outcomes, including implantation rate, clinical pregnancy rate, and live birth rate.

Methods: A comprehensive literature review was conducted, focusing on randomized controlled trials, meta-analyses, Cochrane reviews, and recent international guidelines published between 2020 and 2026. The analysis included add-ons commonly utilized in assisted reproductive technology (ART) clinics worldwide. Outcomes assessed included live birth rate, ongoing pregnancy rate, implantation success, patient satisfaction, and cost-effectiveness.

Results: The review demonstrates substantial heterogeneity in both clinical practice and evidence quality. Certain interventions, such as preimplantation genetic testing for aneuploidy (PGT-A) in selected patient populations and blastocyst culture, may provide benefit under specific clinical circumstances. However, many widely marketed add-ons lack strong evidence of improved live birth rates. Several interventions showed conflicting or insufficient evidence. Endometrial scratching demonstrated no consistent improvement in live birth outcomes in unselected populations. Immunological treatments, including intralipid therapy and corticosteroids, remain controversial because of limited high-quality evidence. Time-lapse imaging may improve the embryo selection workflow but has not consistently demonstrated superior live-birth outcomes compared with conventional incubation. Endometrial receptivity analysis (ERA) and platelet-rich plasma (PRP) therapy continue to generate debate, particularly in patients with

recurrent implantation failure. The analysis also highlights a growing ethical concern regarding the commercialization of unproven interventions and the psychological vulnerability of infertile couples seeking maximal treatment optimization.

Conclusions: Although IVF add-ons are increasingly integrated into modern reproductive medicine, many interventions continue to outpace the scientific evidence supporting their routine use. Evidence-based counseling, individualized patient selection, transparency regarding success probabilities, and careful cost-benefit assessment remain essential in ART practice. Future large-scale randomized trials focusing on live birth as the primary endpoint are necessary to establish the true clinical value of these adjunctive therapies.

Keywords: assisted reproductive technology; endometrial receptivity analysis; evidence-based medicine; implantation failure; immunotherapy; in vitro fertilization; IVF add-ons; platelet-rich plasma; preimplantation genetic testing for aneuploidy; reproductive medicine.

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EFFECT OF PRECONCEPTION GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST THERAPY ON ASSISTED REPRODUCTIVE TECHNOLOGY OUTCOMES IN WOMEN WITH OBESITY: A PROSPECTIVE CONTROLLED STUDY

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ABSTRACT

Background: This study evaluated whether preconception glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy improves assisted reproductive technology (ART) outcomes in women with obesity. Preconception GLP-1 RA therapy was associated with reductions in BMI, improvements in metabolic parameters and ovarian response, and higher clinical pregnancy and live birth rates. Obesity negatively affects fertility and ART outcomes through mechanisms such as insulin resistance, chronic low-grade inflammation, altered endometrial receptivity, and hormonal dysregulation. GLP-1 RAs, including Tirzepatide and Semaglutide, promote weight loss, improved insulin sensitivity, and reduction of systemic inflammation. However, their preconception use and impact on ART outcomes (IVF/ICSI success rates, implantation, live birth) remain insufficiently studied.

Methods: 36 patients on Semaglutide+Metformin preconception treatment were included in study group 1, and 42 patients on Tirzepatide+Metformin preconception treatment were included in study group 2. The control group consisted of 42 patients on lifestyle modification+metformin therapy. ART Procedure included controlled ovarian stimulation (standard protocol), oocyte retrieval, IVF or ICSI, and embryo transfer (fresh or frozen). The primary outcome was clinical pregnancy confirmed by ultrasound. Secondary outcomes were implantation rate, live birth rate, and miscarriage rate. A prospective controlled cohort study was conducted at GGRC clinics (Tbilisi, Georgia) from January 2024 to January 2026.

Results: Mean reduction of BMI before ART in group 1 (6.3 ± 1.0 kg/m²) and in group 2 (6.5 ± 0.8 kg/m²) was significantly higher compared to the control group (1.9 ± 1.8 kg/m²; $p1-C<0.001$; $p2-C<0.001$). Mean reduction of HOMA-IR before ART in group 1 was 1.7 ± 1.2 , and in group 2 – 1.9 ± 0.7 . The latter was significantly higher compared to the control group (1.9 ± 1.0). Clinical pregnancy in group 1 occurred in 27 cases (75.0%); in group 2 – 34 cases (81.0%); in the control group – 20 cases (47.6%, $p1-C=0.014$; $p2-C=0.002$). Live birth in group 1 was observed in 26 cases (72.2%); in group 2, in 31 cases (73.8%); and in the control group, in 18 cases (42.9%; $p1-C=0.010$; $p2-C=0.005$).

Conclusion: The small sample size, non-randomized design, short follow-up period, and the participants' age (30+ years) may be considered limitations of the study. The study findings may support a shift in fertility care toward a more preventive and personalized model. Preconception therapy with GLP-1 RA could represent a promising strategy for metabolic optimization in women with obesity. This approach has the potential to complement or enhance conventional lifestyle-based recommendations. However, larger RCTs are required.

Keywords: obesity; assisted reproductive technology; GLP-1 receptor agonists; preconception care; in vitro fertilization; live birth; insulin resistance.

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DELAYED OVULATION AFTER HCG TRIGGER IN PCOS: SUCCESSFUL DONOR IUI FOLLOWING INDIVIDUALIZED TIMING

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ABSTRACT

Background: Intrauterine insemination (IUI) with ovulation induction is a common fertility treatment for women with anovulation, particularly those with polycystic ovary syndrome (PCOS). A typical IUI protocol assumes that ovulation occurs approximately 36-40 hours after administration of human chorionic gonadotropin (hCG). However, individual variation in ovulatory response may lead to treatment failure or suboptimal timing of insemination.

Case Presentation: A 25-year-old woman with irregular menstrual cycles and polycystic ovarian morphology sought pregnancy through donor sperm insemination. Following letrozole treatment, dominant follicular development was not achieved during the initial treatment cycle. After three months of pretreatment with metformin and combined oral contraceptives, successful follicular maturation was obtained. Serial transvaginal ultrasonography demonstrated a dominant follicle measuring 20-22 mm and an endometrial thickness of 9-10 mm before ovulation was triggered with urinary hCG (Pubergen 5000 IU). During the first insemination cycle, follicular rupture was not observed within the expected period following hCG administration. Serial ultrasonography subsequently demonstrated follicular rupture approximately 55 hours after hCG administration, accompanied by follicular collapse and accumulation of free fluid in the pouch of Douglas. Delayed ovulation was consistently observed during the first three IUI cycles. Based on these findings, insemination timing was individualized in the subsequent cycle to correspond with the patient’s ovulatory response. Estrogen and, where clinically indicated, low-dose aspirin and progesterone during the luteal phase were used as adjunctive therapy. Fourteen days after insemination, serum β-hCG testing was positive, confirming pregnancy. Follow-up transvaginal ultrasonography demonstrated an intrauterine pregnancy with a gestational sac and fetal cardiac activity.

Discussion: This case highlights the clinical importance of recognizing individual variation in ovulatory kinetics during fertility treatment. The patient consistently demonstrated follicular rupture approximately 55 hours after hCG administration, rather than the expected interval of 36-

40 hours. Failure to recognize this delayed response could result in suboptimal insemination timing and unsuccessful treatment cycles. Individualized scheduling based on serial ultrasonographic monitoring may improve outcomes in selected women with PCOS.

Conclusions: Delayed ovulation following hCG administration should be considered in women with PCOS who demonstrate atypical responses to ovulation induction. This case emphasizes the value of serial ultrasonographic monitoring and individualized insemination timing, which, in this patient, was associated with successful conception following previous unsuccessful cycles using conventional timing.

Keywords: delayed ovulation; human chorionic gonadotropin; intrauterine insemination; ovulation induction; polycystic ovary syndrome.

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ASSISTED REPRODUCTIVE TECHNOLOGIES: CHALLENGES OF THE 21ST CENTURY

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ABSTRACT

Background: Infertility remains one of the most pressing medical and demographic issues of the 21st century. According to WHO data, one in six couples worldwide faces the challenge of conception or pregnancy loss. Under these conditions, assisted reproductive technologies (ART) are transforming from a specialized field of medicine into a vital instrument of national demographic policy. The modern phase of ART development is characterized by a paradigm shift: moving from simply evaluating pregnancy rates to ensuring maximum safety and the birth of a healthy child. Elective single embryo transfer (eSET) has become the gold standard of care, minimizing the risks of multiple pregnancies and associated perinatal complications.

Methods: The integration of advanced technologies drives the high efficacy of modern IVF programs:

- * Innovative Embryology: Application of artificial intelligence (AI) systems and time-lapse incubators for objective, continuous monitoring of embryonic development.
- * Genetic Screening: Widespread adoption of preimplantation genetic testing for aneuploidies (PGT-A) to select euploid embryos, significantly reducing reproductive losses.
- * Fertility Preservation: Advances in oocyte and ovarian tissue vitrification, applied both for medical reasons (oncofertility) and social family planning amid global trends toward delayed parenthood.

Results: Ensuring access to reproductive healthcare is of paramount importance. The execution of state-sponsored initiatives, such as Kazakhstan’s `Ansagan Sabi~` program, demonstrates that public funding for ART directly correlates with increased birth rates and reduced social tension. However, the rapid progress of ART continues to outpace regulatory frameworks. Establishing robust bioethical and legal standards regarding gamete donation, surrogacy, long-term cryopreserved biomaterial storage, and emerging genome-editing capabilities remains a critical challenge.

Conclusion: The future of ART lies in personalized medicine, granular evaluation of endometrial receptivity, and tight interdisciplinary collaboration among reproductive endocrinologists, embryologists, geneticists, and andrologists. A comprehensive approach addressing technological, financial, and legal barriers will enable ART to effectively meet the demographic challenges of the modern era.

Keywords: Assisted reproductive technologies (ART); in vitro fertilization (IVF); elective single embryo transfer (eSET); preimplantation genetic testing for aneuploidy (PGT-A); fertility preservation; reproductive health policy

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INTERDISCIPLINARY ASPECTS OF MALE INFERTILITY AS A COMORBID CONDITION: A REPRODUCTIVE SPECIALIST’S PERSPECTIVE

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ABSTRACT

Background: Male infertility affects 12-17% of couples in Kazakhstan, with no declining trend worldwide. The use of assisted reproductive technologies (ART) increasingly neutralizes natural selection, raising concerns about fertilization by spermatozoa with compromised chromatin integrity. Contemporary male reproductive health is further challenged by a non-infectious epidemic of “civilization diseases” – obesity, type 2 diabetes, metabolic syndrome, chronic stress, and cardiovascular pathology – often emerging alongside age-related androgen deficiency after age 30-40.

Sperm DNA fragmentation (DFI) has emerged as one of the most severe and difficult-to-treat forms of male infertility. However, the pathophysiological mechanisms underlying DNA damage remain incompletely understood, and ART methods such as IVF, ICSI, and IMSI do not always yield successful outcomes. To evaluate the prevalence and etiology of elevated sperm DNA fragmentation in infertile men and to assess the efficacy of interdisciplinary, pathogenetically oriented diagnostic and therapeutic approaches, including magnetic-activated cell sorting (MACS).

Methods: A prospective study was conducted at KRAS Clinic (Almaty) from 2023 to 2024, enrolling 360 male patients aged 22-38 years from infertile couples. Comprehensive evaluation included: semen analysis per WHO 6th edition (2021) using CASA; sperm DNA fragmentation assessed by flow cytometry (SCSA); hormonal profiling (FSH, LH, PRL, TSH, anti-TPO, anti-TG, total testosterone, SHBG, insulin); biochemical markers (HbA1c, triglycerides, homocysteine); infectious screening; and imaging studies. A separate cohort of 63 patients with oligoastheno-teratozoospermia underwent MACS to evaluate its effect on DFI.

Results: High DNA fragmentation (DFI >30%) was identified in 77% of patients (n=277). Normozoospermia was observed in only 18.4%, while 34% presented with combined forms of pathospermia. The study revealed a systemic environment of chronic inflammation, oxidative stress, and hormonal imbalance – particularly thyroid dysfunction and metabolic syndrome – as key drivers of spermatogenic damage.

In the MACS cohort, magnetic-activated cell sorting significantly reduced DNA fragmentation from 32.4% to 10.5%, demonstrating its efficacy in selecting genetically intact spermatozoa for ART. A clinical case is presented: a couple with 9 previous failed IVF cycles and extensive male comorbidities (including metabolic syndrome, NAFLD, chronic prostatitis, and Hepatitis C in remission) achieved successful pregnancy and live birth following comprehensive pathogenetic therapy and MACS-assisted sperm selection.

Conclusion: Elevated DFI is not merely a sperm parameter but the “tip of the iceberg” of systemic comorbid disorders. The emerging paradigm of the Gut-Liver-Testis axis positions microbiome dysbiosis, metabolic inflammation, and mitochondrial dysfunction as root sources of oxidative stress. “Idiopathic” male infertility, viewed through an interdisciplinary lens, is treatable hormonal-metabolic infertility requiring comprehensive diagnostics and pathogenetic therapy – sufficient either for natural conception or as preparation for ART.

Diagnosis and treatment of male infertility today demand an interdisciplinary team approach integrating reproductive specialists, endocrinologists, urologists, gastroenterologists, and geneticists. As the paternal genome epigenetically determines not only fertilization and pregnancy outcomes but also offspring health, we treat not one patient but two generations. The XXI century calls for pathogenetic and preventive medicine – a shift from symptomatic DFI management to correction of underlying systemic diseases.

Keywords: male infertility, sperm DNA fragmentation, oxidative stress, metabolic syndrome, MACS, interdisciplinary approach, comorbid conditions.

Declarations

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ASSESSMENT OF RHEOLOGICAL STATUS IN A PREGNANT PATIENT WITH HEART FAILURE: A CLINICAL CASE REPORT

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ABSTRACT

Background: Pregnancy in patients with heart failure represents a complex clinical condition associated with significant hemodynamic changes and increased cardiovascular stress. Alterations in blood rheology, including changes in blood viscosity, erythrocyte deformability, and microcirculatory function, may influence tissue perfusion, cardiac workload, and the progression of cardiovascular complications during pregnancy. This clinical case report evaluates the significance of assessing rheological status in a pregnant patient with heart failure and discusses its potential role in individualized monitoring and management.

Methods: A clinical case of a pregnant patient with heart failure was analyzed. The assessment included clinical examination, cardiovascular evaluation, standard laboratory investigations, and analysis of hemorheological parameters reflecting blood viscosity, erythrocyte aggregation, and microcirculatory characteristics. The findings were interpreted in relation to the patient’s hemodynamic status and pregnancy-associated physiological adaptations.

Results: The patient demonstrated alterations in rheological parameters associated with impaired blood flow properties and increased cardiovascular load. Changes in hemorheological status were considered relevant for evaluating circulatory adaptation and the potential risks of impaired tissue perfusion. Comprehensive assessment, combining cardiac function evaluation and rheological monitoring, provided additional information to support clinical decision-making and optimize therapeutic strategies. Individualized management, including careful hemodynamic observation and multidisciplinary follow-up, contributed to improved control of maternal cardiovascular status.

Conclusions: Assessment of rheological status may represent a valuable complementary approach in pregnant patients with heart failure, providing additional insight into microcirculatory changes and cardiovascular adaptation. Integration of hemorheological evaluation with conventional cardiac monitoring may improve risk assessment and support personalized management strategies. Further clinical studies are needed to determine standardized rheological markers and their prognostic significance in pregnancy complicated by heart failure.

Keywords: blood viscosity; cardiovascular adaptation; clinical case report; heart failure; hemodynamic monitoring; hemorheology; maternal cardiovascular disease; microcirculation; pregnancy; rheological status.

Declarations

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CURRENT EXPERIENCE OF BAU INTERNATIONAL UNIVERSITY IN THE SURGICAL MANAGEMENT OF POSTPARTUM HEMORRHAGE USING INTERNAL ILIAC ARTERY LIGATION

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ABSTRACT

Background: Postpartum hemorrhage (PPH) remains the leading cause of preventable maternal mortality worldwide. Although pharmacological therapy and uterus-preserving techniques are considered first-line treatments, surgical interventions remain indispensable when conservative measures fail. Bilateral internal iliac artery ligation (IIAL) is an established fertility-preserving procedure that significantly reduces pelvic arterial blood flow and facilitates hemostasis in severe obstetric hemorrhage. This review evaluates the clinical role and effectiveness of internal iliac artery ligation in managing postpartum hemorrhage and highlights the contributions of multidisciplinary research supported by BAU International University.

Methods: This study presents a narrative review of current evidence together with institutional clinical experience regarding the use of IIAL in patients with severe postpartum hemorrhage. Particular attention was given to surgical indications, procedural technical aspects, perioperative outcomes, fertility preservation, and integration with modern multidisciplinary management protocols. The research was conducted as part of scientific initiatives supported by BAU International University, which promote collaboration among obstetricians, vascular surgeons, anesthesiologists, and academic researchers.

Results: Internal iliac artery ligation remains an effective uterus-preserving surgical option for controlling life-threatening postpartum hemorrhage when medical therapy and conservative surgical measures are unsuccessful. Successful application of IIAL reduces intraoperative blood loss, decreases the need for hysterectomy, and improves maternal outcomes while preserving future reproductive potential. Optimal results are achieved through early decision-making, experienced surgical teams, standardized hemorrhage protocols, and multidisciplinary cooperation. Institutional support from BAU International University has facilitated clinical research, surgical education, and the development of evidence-based approaches to obstetric hemorrhage management.

Conclusions: Internal iliac artery ligation continues to play a valuable role in the comprehensive management of postpartum hemorrhage, particularly in resource-limited settings and com-

plex obstetric emergencies. Ongoing academic collaboration and institutional support from BAU International University contribute to advancing research, improving surgical expertise, and strengthening evidence-based maternal care.

Keywords: BAU International University; fertility preservation; internal iliac artery ligation; maternal outcomes; multidisciplinary management; obstetric emergency; obstetric hemorrhage; pelvic vascular surgery; postpartum hemorrhage; uterus-preserving surgery.

Declarations

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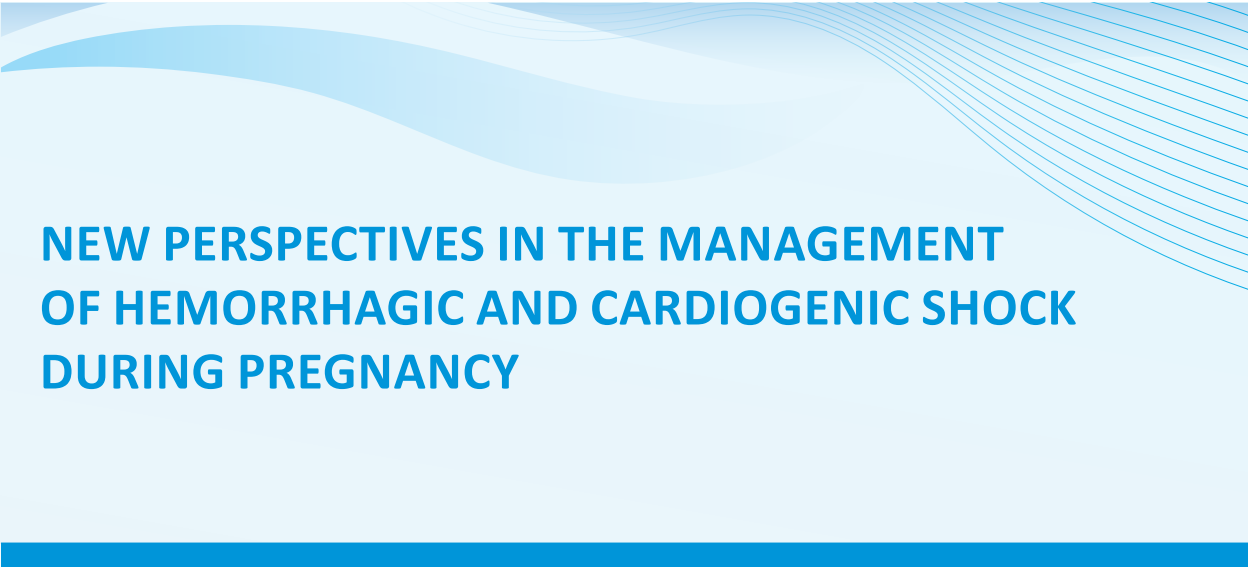
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NEW PERSPECTIVES IN THE MANAGEMENT OF HEMORRHAGIC AND CARDIOGENIC SHOCK DURING PREGNANCY

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ABSTRACT

Background: Hemorrhagic and cardiogenic shock during pregnancy represent critical, life-threatening conditions associated with significant maternal and fetal morbidity and mortality. Pregnancy-related physiological changes in cardiovascular function, blood volume, and coagulation create unique challenges in diagnosis and treatment. Advances in critical care medicine, hemodynamic monitoring, transfusion strategies, and multidisciplinary management have contributed to improved outcomes in obstetric emergencies. This review analyzes current and emerging approaches to the management of hemorrhagic and cardiogenic shock in pregnant patients, focusing on early recognition, individualized resuscitation, and optimization of maternal and fetal outcomes.

Methods: A review of contemporary clinical guidelines and scientific literature was performed, evaluating modern strategies for the diagnosis and treatment of obstetric hemorrhage and pregnancy-associated cardiac failure. The analysis included hemodynamic monitoring, point-of-care ultrasound, blood component therapy, vasoactive support, mechanical circulatory assistance, and multidisciplinary care models.

Results: Early identification of shock through obstetric warning systems, continuous monitoring, and advanced diagnostic technologies enables timely therapeutic intervention. Management of hemorrhagic shock requires rapid control of bleeding, balanced massive transfusion protocols, correction of coagulopathy, administration of tranexamic acid, and appropriate surgical or interventional procedures. Management of cardiogenic shock is based on accurate assessment of cardiac function, optimization of preload and afterload, targeted use of inotropic and vaso-pressor therapy, and treatment of the underlying cardiac pathology. In severe refractory cases, extracorporeal membrane oxygenation (ECMO) and other mechanical circulatory support technologies may provide lifesaving options. Successful outcomes depend on coordinated teamwork among obstetricians, anesthesiologists, cardiologists, intensivists, and neonatologists.

Conclusions: Modern management of hemorrhagic and cardiogenic shock during pregnancy requires rapid diagnosis, evidence-based resuscitation protocols, personalized hemodynamic

strategies, and access to advanced critical care technologies. Integration of multidisciplinary approaches and innovative therapeutic methods offers new opportunities to reduce maternal and neonatal complications and improve survival.

Keywords: cardiogenic shock; extracorporeal membrane oxygenation; hemodynamic monitoring; hemorrhagic shock; massive transfusion; maternal critical care; multidisciplinary management; obstetric emergency; postpartum hemorrhage; pregnancy.

Declarations

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RHEOLOGICAL STATUS AND RISKS OF HEMORRHAGIC SHOCK DURING PHYSIOLOGICAL PREGNANCY

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ABSTRACT

Background: Pregnancy is accompanied by significant physiological adaptations in the cardiovascular and hemostatic systems, including changes in blood volume, plasma composition, coagulation activity, and blood rheology. These alterations are essential for maintaining adequate uteroplacental circulation but may also influence the response to acute blood loss and the development of hemorrhagic shock during obstetric emergencies. This review evaluates the characteristics of rheological changes during physiological pregnancy and their potential role in assessing the risk of hemorrhagic shock in obstetric practice.

Methods: A review of current scientific data was conducted to analyze changes in hemorheological parameters during normal pregnancy, including blood viscosity, erythrocyte deformability, erythrocyte aggregation, and plasma viscosity, and their relationship to hemostatic balance. The potential significance of these parameters for predicting the severity of blood loss and adaptive capacity during postpartum hemorrhage was assessed.

Results: Physiological pregnancy is characterized by increased plasma volume, changes in erythrocyte properties, and a progressive hypercoagulable state that protects against excessive bleeding during delivery. However, disturbances in rheological balance, endothelial function, and microcirculatory regulation may contribute to impaired tissue perfusion and reduced compensatory capacity during acute hemorrhage. Assessment of rheological status may provide additional information to identify pregnant patients at increased risk of hemodynamic instability. Integration of hemorheological markers with conventional clinical monitoring could improve risk stratification and support individualized approaches to the prevention and management of obstetric hemorrhage.

Conclusions: Rheological status represents an important component of physiological adaptation during pregnancy and may influence the development and severity of hemorrhagic shock. Further research is required to establish standardized rheological indicators for the early prediction of obstetric bleeding complications and to incorporate them into modern maternal care protocols.

Keywords: blood viscosity; coagulation; erythrocyte deformability; hemorheology; hemorrhagic shock; maternal hemodynamics; microcirculation; obstetric risk assessment; postpartum hemorrhage; pregnancy.

Declarations

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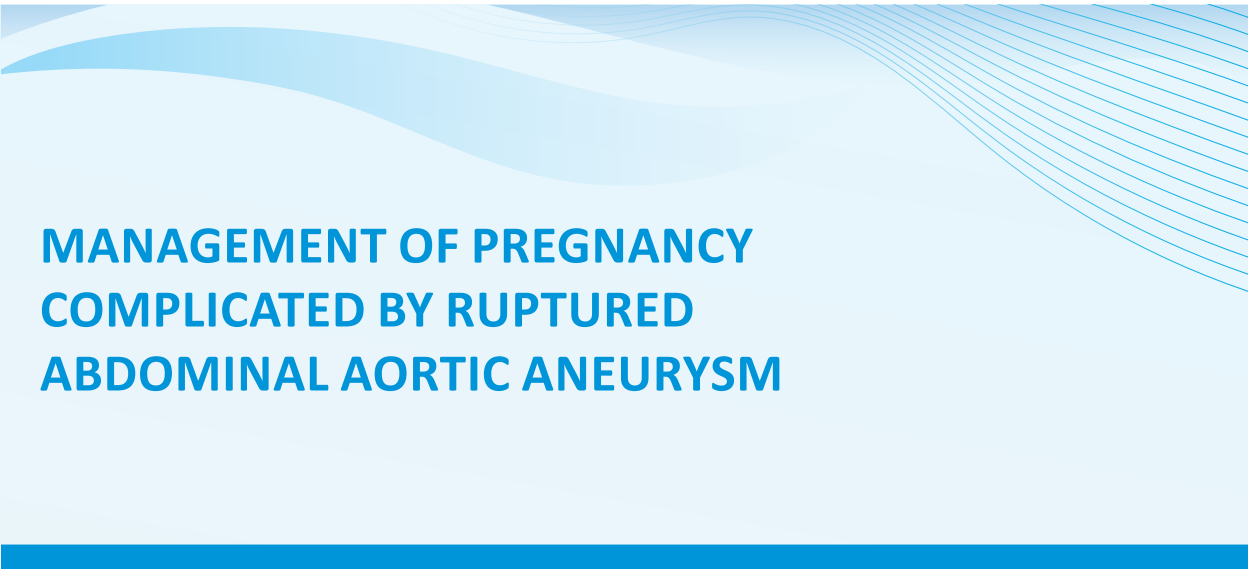
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MANAGEMENT OF PREGNANCY COMPLICATED BY RUPTURED ABDOMINAL AORTIC ANEURYSM

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ABSTRACT

Background: Ruptured abdominal aortic aneurysm (AAA) during pregnancy is an extremely rare but catastrophic vascular emergency associated with high maternal and fetal mortality. Physiological changes during pregnancy, including increased blood volume, cardiac output, and hormonal effects on the vascular wall, may contribute to aneurysm expansion and rupture. Early diagnosis and coordinated multidisciplinary management are essential for improving outcomes. This review examines current approaches to the diagnosis and management of pregnancy complicated by ruptured abdominal aortic aneurysm, with emphasis on maternal stabilization, surgical decision-making, and fetal considerations.

Methods: A review of available clinical evidence and reported cases was performed, focusing on diagnostic strategies, emergency surgical interventions, vascular repair techniques, anesthetic management, and obstetric outcomes. Particular attention was given to the role of multidisciplinary teams involving vascular surgeons, obstetricians, anesthesiologists, intensivists, and neonatologists.

Results: The clinical presentation of ruptured abdominal aortic aneurysm during pregnancy may be nonspecific and can mimic common obstetric or abdominal conditions, leading to delays in diagnosis. Rapid assessment with appropriate imaging modalities, including ultrasonography and, when clinically justified, computed tomography, is crucial. Emergency management requires simultaneous maternal resuscitation, hemorrhage control, and individualized decisions regarding continuation of the pregnancy or delivery. Open surgical repair remains the traditional treatment option, while endovascular techniques may represent an alternative in selected cases depending on gestational age, anatomical characteristics, and available expertise. Continuous maternal hemodynamic monitoring and fetal assessment are essential components of care.

Conclusions: Ruptured abdominal aortic aneurysm during pregnancy remains a rare but life-threatening condition requiring immediate recognition and multidisciplinary intervention. Successful outcomes depend on early diagnosis, rapid vascular control, an individualized sur-

gical strategy, and coordinated obstetric and critical care management. The establishment of specialized protocols may improve maternal and fetal survival in these challenging cases.

Keywords: abdominal aortic aneurysm; aneurysm rupture; endovascular repair; hemodynamic stabilization; maternal mortality; multidisciplinary care; obstetric management; pregnancy; vascular emergency; vascular surgery.

Declarations

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RADIOTHERAPY-ASSOCIATED COMPLICATIONS IN PATIENTS WITH MALIGNANT PROSTATE NEOPLASMS

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ABSTRACT

Background: Radiotherapy is a well-established treatment modality for localized and locally advanced prostate cancer, offering excellent oncological outcomes while preserving organ function. However, radiation-induced toxicity remains a significant clinical concern and may adversely affect patients’ quality of life. Early recognition and appropriate management of radiotherapy-associated complications are essential for optimizing treatment outcomes. This review examines the spectrum, frequency, and clinical impact of radiotherapy-associated complications in patients with malignant prostate neoplasms and highlights current approaches to their prevention and management.

Methods: A review of published clinical evidence and current treatment practices was performed, focusing on acute and late complications following external beam radiotherapy and brachytherapy for prostate cancer. Reported adverse events involving the genitourinary, gastrointestinal, and sexual systems were evaluated, together with factors influencing their occurrence and severity.

Results: Acute complications commonly included urinary frequency, dysuria, urgency, nocturia, mild hematuria, diarrhea, rectal discomfort, and fatigue. Most acute adverse effects were transient and responded to conservative management. Late complications, although less frequent, had a greater impact on long-term quality of life and included radiation cystitis, urethral stricture, chronic proctitis, rectal bleeding, urinary incontinence, erectile dysfunction, and, rarely, fistula formation. The incidence and severity of toxicity were influenced by radiation dose, treatment technique, patient age, baseline urinary function, comorbidities, and concomitant therapies. Modern radiotherapy techniques, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and advanced treatment planning, have significantly reduced radiation exposure to surrounding normal tissues and lowered the incidence of severe complications.

Conclusions: Radiotherapy remains a safe and effective treatment for prostate cancer when delivered using contemporary techniques. Careful patient selection, individualized treatment planning, regular follow-up, and early management of treatment-related adverse events are critical for minimizing complications and maintaining patients' quality of life. A multidisciplinary approach involving radiation oncologists, urologists, and supportive care specialists is essential for achieving optimal clinical outcomes.

Keywords: brachytherapy; external beam radiotherapy (EBRT); gastrointestinal complications; genitourinary complications; intensity-modulated radiotherapy (IMRT); prostate cancer; prostate neoplasms; quality of life; radiation-induced toxicity; radiotherapy.

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ABSTRACT

Background: Breast cancer ranks first among women in most countries in terms of both incidence and mortality. Surgical treatment has traditionally been the cornerstone of breast cancer management. The widespread implementation of mammographic screening has led to an increased detection rate of early-stage tumors. Together with the growing number of younger patients, this has created a greater demand for breast-conserving surgical approaches. This study evaluated the oncological outcomes, postoperative complications, and aesthetic outcomes in patients with breast cancer who underwent breast-conserving surgery.

Methods: A total of 265 patients with breast cancer who received comprehensive treatment at the Oncology Clinic of Azerbaijan Medical University between 2022 and 2025 were retrospectively evaluated. The mean age of the patients was 56 years. Among the 265 patients, 105 underwent radical breast resection, 5 underwent quadrantectomy with axillary lymph node dissection, and 155 underwent lumpectomy with axillary lymph node dissection. Contralateral breast reduction for symmetry was performed in 105 patients. In addition, tissue displacement techniques were used in 15 patients with tumors located in the inner quadrants to reconstruct the postoperative defect. Disease stages were distributed as follows: Stage 0, 3 patients (1.1%); Stage I, 113 (42.6%); Stage IIA, 96 (36.2%); Stage IIB, 29 (10.9%); Stage IIIA, 23 (8.7%); and Stage IIIB, 1 patient (0.4%). Histopathological subtypes included invasive carcinoma in 164 patients (61.9%), ductal carcinoma in situ in 81 (30.6%), invasive lobular carcinoma in 14 (5.3%), and mixed histological types in 6 patients (2.3%). According to molecular subtype, 103 patients (38.9%) had Luminal A tumors, 81 (30.6%) had Luminal B tumors, 42 (15.8%) had HER2-positive tumors, and 39 (14.7%) had triple-negative breast cancer. All patients received postoperative radiotherapy. Neoadjuvant chemotherapy was administered to 123 patients, including 19 (15.4%) with Luminal A, 23 (18.7%) with Luminal B, 42 (34.1%) with HER2-positive, and 39 (31.7%) with triple-negative tumors. Adjuvant endocrine therapy was prescribed to 131 hormone receptor-positive patients, of whom 74 (56.5%) additionally underwent medical ovarian suppression.

Results: During the 5-year follow-up period, local recurrence was observed in 8 patients (3.0%): 1 patient (0.4%) with Stage I disease, 6 patients (2.3%) with Stage II disease, and 1 patient (0.4%) with Stage III disease. Poor prognostic factors associated with recurrence included grade 2-3 invasive ductal carcinoma, the presence of tumor emboli within peritumoral vessels, and microscopic foci of carcinoma surrounding the primary tumor.

Conclusions: During the 5-year follow-up period, local recurrence occurred in 8 patients (3.0%) after breast-conserving surgery. The recurrence rate was associated with both the tumor's histopathological characteristics and the disease stage.

Keywords: axillary lymph node dissection; breast cancer; breast-conserving surgery; lumpectomy; neoadjuvant chemotherapy; oncological outcomes; radiotherapy; recurrence; surgical treatment.

Declarations

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REGENERATIVE THERAPIES IN IVF: CLINICAL AND BIOLOGICAL IMPACT OF PRP, MESENCHYMAL STEM CELLS, AND EXOSOMES ON OVARIAN FUNCTION

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ABSTRACT

Background: Diminished ovarian reserve (DOR) remains a significant barrier in reproductive medicine, driving interest in regenerative strategies to enhance ovarian function. Platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), and exosome-based therapies have been proposed as potential interventions due to their roles in tissue repair, cellular signaling, and follicular activation. This review evaluates current evidence on the clinical efficacy, underlying biological mechanisms, and translational potential of these regenerative modalities in assisted reproductive technologies (ART).

Materials and Methods: A structured analysis of meta-analyses, clinical studies, and preclinical research was performed. PRP outcomes were assessed through changes in anti-Mullerian hormone (AMH), antral follicle count (AFC), oocyte yield, embryo development, and pregnancy rates. Evidence for MSC and exosome therapies was synthesized from molecular and histological studies focusing on microRNA regulation, inflammatory modulation, and ovarian tissue regeneration. Comparative evaluation emphasized clinical applicability and readiness for translation.

Results: PRP demonstrated consistent short-term improvements in ovarian reserve markers, with AMH increases at 1, 2, and 3 months (+0.20, +0.26, +0.36 ng/mL) and an average AFC rise of 1.60 follicles. Enhanced oocyte retrieval and embryo numbers were reported, alongside biochemical pregnancy (18%), spontaneous pregnancy (7%), and live birth (11%). MSC-based therapies showed regenerative potential by modulating microRNAs and exosomal miRNAs involved in cellular repair and follicular activation. Exosome therapies have shown early evidence of ovarian tissue regeneration, though their in vivo mechanisms and safety profiles remain poorly defined.

Conclusion: PRP currently represents the most clinically applicable regenerative intervention in IVF. MSC and exosome therapies hold substantial biological promise but require rigorous clinical validation and protocol standardization. Regenerative medicine may offer future therapeutic opportunities for managing DOR and age-related infertility.

Keywords: antral follicle count; assisted reproductive technologies; diminished ovarian reserve; exosomes; mesenchymal stem cells; ovarian regeneration; platelet-rich plasma; regenerative medicine.

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ENDOMETRIAL MICROBIOME AND RECURRENT IMPLANTATION FAILURE AFTER TRANSFER OF PGT-A EUPLOID EMBRYOS: IS THERE A MISSING LINK?

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ABSTRACT

Background: Recurrent implantation failure (RIF) remains a significant clinical challenge despite advances in assisted reproductive technology. The transfer of a morphologically high-quality, PGT-A-confirmed euploid embryo substantially reduces embryonic causes of implantation failure, thereby shifting attention toward endometrial factors. Among these, the endometrial microbiome has emerged as a potential regulator of endometrial receptivity by influencing local immune homeostasis, inflammatory signaling, epithelial integrity, and embryo-endometrial communication. However, the clinical significance of microbiome alterations in women experiencing repeated failure after euploid embryo transfer remains controversial.

Objective: To critically review current evidence regarding the association between endometrial microbiome composition and recurrent implantation failure following transfer of PGT-A euploid embryos, and to evaluate whether available data support a causal relationship or a clinically actionable diagnostic and therapeutic target.

Methods: A narrative, evidence-based review of the published literature indexed in PubMed, Embase, and the Cochrane Library was conducted. Meta-analyses, systematic reviews, prospective cohort studies, and randomized controlled trials evaluating endometrial microbiome profiling, implantation outcomes, and reproductive success after euploid embryo transfer were included. Particular attention was given to studies using next-generation sequencing (16S rRNA sequencing and metagenomic approaches), standardized RIF definitions, and validated reproductive outcomes.

Results: Current evidence suggests that the endometrial microbiome is characterized by low microbial biomass and substantial inter-individual variability, creating important methodological challenges and increasing susceptibility to contamination during sample collection and sequencing. Although several observational studies have reported lower implantation and live birth rates in women with non-Lactobacillus-dominant microbiota, subsequent investigations have produced conflicting findings.

Importantly, studies specifically evaluating women undergoing transfer of PGT-A euploid embryos remain limited and heterogeneous. Differences in sequencing methodologies, diagnostic thresholds, sampling timing, antibiotic exposure, hormonal environment, and definitions of dysbiosis contribute to inconsistent results. Furthermore, no universally accepted definition of a “healthy” endometrial microbiome currently exists.

Randomized evidence demonstrating improved reproductive outcomes following microbiome-targeted interventions, including antibiotics, probiotics, or microbiome-guided treatment strategies, is currently lacking. Major reproductive societies therefore do not recommend routine endometrial microbiome testing in the evaluation of recurrent implantation failure outside research settings.

Conclusions: The endometrial microbiome represents a biologically plausible contributor to implantation success after transfer of euploid embryos; however, current evidence remains insufficient to establish a causal relationship between microbial composition and recurrent implantation failure. Existing data are predominantly observational and are limited by methodological heterogeneity and lack of standardized diagnostic criteria.

Future multicenter prospective studies integrating microbiome analysis with immune profiling, transcriptomics, metabolomics, and endometrial receptivity biomarkers are needed to determine whether the endometrial microbiome represents a true therapeutic target or merely reflects the underlying endometrial environment. At present, routine clinical implementation of endometrial microbiome testing for patients with recurrent implantation failure after euploid embryo transfer cannot be recommended outside well-designed clinical trials.

Keywords: assisted reproductive technology; endometrial microbiome; endometrial receptivity; euploid embryo; implantation; PGT-A; recurrent implantation failure; reproductive immunology.

Declarations

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BEYOND CONVENTIONAL PGT:
INTEGRATING POLYGENIC RISK ANALYSIS INTO
PGT-A AND PGT-M A SYSTEMATIC REVIEW
OF CLINICAL UTILITY, TECHNICAL CHALLENGES,
AND ETHICAL CONSIDERATIONS

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ABSTRACT

Background: Advances in genome-wide genotyping, next-generation sequencing, and polygenic risk score modeling have created new opportunities for extending preimplantation genetic testing beyond conventional PGT-A and PGT-M. Preimplantation genetic testing for polygenic disorders, also referred to as PGT-P, aims to estimate an embryo’s relative genetic susceptibility to common multifactorial diseases by simultaneously analyzing multiple genomic variants. Unlike PGT-M, which is used for monogenic disorders with clearly defined pathogenic variants, PGT-P provides probabilistic risk estimates for conditions influenced by both genetic and environmental factors. Proposed applications include embryo prioritization according to predicted risk for diseases such as type 2 diabetes, cardiovascular disease, schizophrenia, and selected cancers. However, the clinical value, technical robustness, predictive validity, and ethical acceptability of this approach remain highly debated. This systematic review evaluates the current evidence on integrating polygenic risk analysis into PGT-A and PGT-M workflows, with particular emphasis on clinical utility, technical limitations, and ethical implications in assisted reproductive technology.

Methods: A systematic narrative review was conducted using peer-reviewed literature published between 2019 and 2026 and identified through PubMed, Scopus, and relevant professional society statements. Special attention was given to recent reviews on PGT-P and to the American College of Medical Genetics and Genomics points-to-consider statement addressing the clinical utility of polygenic risk score-based embryo selection. Studies and position papers related to genome-wide association studies, embryo genotyping platforms, PRS algorithms, embryo ranking strategies, ancestry-related performance differences, and ethical frameworks were reviewed. Technical factors, including embryo biopsy, whole-genome amplification, allele drop-out, genotyping accuracy, sibling embryo comparison, and population stratification, were also examined.

Results: Current evidence suggests that PGT-P is technically achievable and can be used to generate relative polygenic risk estimates among sibling embryos. PRS-based embryo ranking

may theoretically reduce the probability of selected multifactorial diseases in future offspring. However, available data indicate that the expected benefit is generally modest, largely because sibling embryos inherit genomes from the same two parents and therefore show limited genetic variation compared with unrelated individuals. The predictive performance of PRS is also strongly influenced by ancestry, with reduced accuracy in populations underrepresented in GWAS datasets. Additional limitations include technical noise introduced by trophectoderm biopsy and whole-genome amplification, differences between PRS algorithms, incomplete reproducibility across laboratories, and uncertainty in translating population-level risk models to individual embryos. Furthermore, most polygenic diseases are shaped by environmental exposures, lifestyle, epigenetic regulation, and gene-environment interactions, limiting the deterministic interpretation of embryo PRS results. Ethical concerns include embryo commodification, widening of social inequalities, expansion toward non-medical trait selection, stigmatization of disease-associated genetic profiles, and the risk of creating unrealistic expectations among prospective parents. Professional organizations, including ACMG and ASRM, currently indicate that the evidence base is insufficient to support the routine clinical use of PGT-P for embryo selection outside research or carefully regulated contexts.

Conclusions: PGT-P is an emerging yet clinically immature extension of reproductive genetics. Although polygenic risk analysis may eventually provide complementary information alongside established PGT-A and PGT-M approaches, its current use is constrained by biological complexity, technical uncertainty, limited predictive power, ancestry-related bias, and unresolved ethical challenges. PRS-based embryo ranking should therefore be interpreted cautiously, particularly for multifactorial diseases with strong environmental components and in populations not well represented in existing genomic datasets. Future progress will require large-scale, multi-ethnic validation studies, standardized laboratory and bioinformatic workflows, improved accuracy in embryo genotyping, transparent reporting of clinical outcomes, and internationally harmonized ethical and regulatory guidance. Until clear clinical benefit and safety are demonstrated, conventional evidence-based PGT approaches should remain the primary standard for embryo selection in assisted reproductive technology.

Keywords: embryo genotyping; multifactorial diseases; PGT; polygenic risk analysis.

Declarations

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REPRODUCTIVE OPPORTUNITY RATHER THAN EMBRYO NUMBER: INSIGHTS FROM PGT-A IN YOUNG IVF PATIENTS

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ABSTRACT

Background: Embryo cryopreservation has become a cornerstone of fertility preservation, particularly for women planning delayed childbearing. Although young maternal age is generally considered a favorable prognostic factor, neither age nor embryo morphology reliably predicts chromosomal competence. This study aimed to evaluate whether preimplantation genetic testing for aneuploidy (PGT-A) provides a more clinically meaningful estimate of future reproductive opportunity than the total number of cryopreserved embryos in women younger than 35 years undergoing in vitro fertilization (IVF).

Methods: A retrospective single-center study was conducted at the Georgian-German Reproduction Center (GGRC), Tbilisi, Georgia, including women aged 24-35 years who underwent IVF with PGT-A between 2020 and 2025. Eligible patients had anti-Mullerian hormone levels of 2-5 ng/mL, body mass index of 18.5-24.9 kg/m², regular menstrual cycles, and normozoospermic partners. Women with polycystic ovary syndrome, endometriosis, uterine abnormalities, tubal factor infertility, previous ovarian surgery, or severe male factor infertility were excluded. Trophoctoderm biopsy was performed on 566 blastocysts, followed by next-generation sequencing for comprehensive chromosomal analysis.

Results: Of the 566 blastocysts analyzed, 285 (50.4%) were euploid, 127 (22.4%) were aneuploid, 89 (15.7%) demonstrated low-level mosaicism, 25 (4.4%) demonstrated high-level mosaicism, and 40 (7.1%) yielded inconclusive results. Despite young maternal age and otherwise favorable reproductive characteristics, only one in two blastocysts was chromosomally normal. These findings suggest that maternal age alone does not reliably predict embryo chromosomal competence and that the total number of cryopreserved embryos may substantially overestimate future reproductive potential when genetic status is unknown.

Conclusion: Among young women undergoing IVF, the number of euploid embryos appears to be a more clinically informative indicator of future reproductive opportunity than the total number of cryopreserved embryos. Incorporating chromosomal status into fertility preservation

counseling may provide patients with more realistic expectations and support more informed reproductive decision-making.

Keywords: aneuploidy; blastocyst; chromosomal competence; euploidy; fertility preservation; trophoctoderm biopsy.

Declarations

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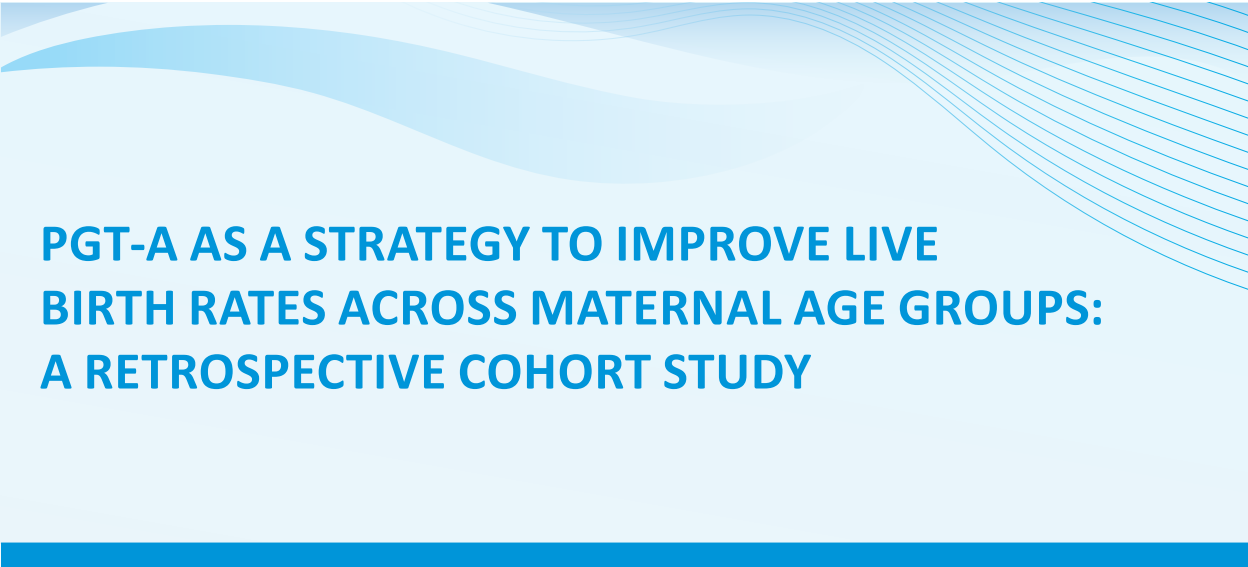
Conflict of Interest: The authors declare no competing interests.

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PGT-A AS A STRATEGY TO IMPROVE LIVE BIRTH RATES ACROSS MATERNAL AGE GROUPS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Advanced maternal age (AMA) is associated with declining oocyte quality, increasing embryo aneuploidy, and reduced reproductive outcomes following in vitro fertilization (IVF). Preimplantation genetic testing for aneuploidy (PGT-A) enables the identification of euploid embryos prior to transfer and may improve reproductive outcomes, particularly in women of advanced maternal age. This study evaluated the association between maternal age and embryo aneuploidy and compared reproductive outcomes after single-embryo transfer (SET) with and without PGT-A.

Methods: This retrospective cohort study included IVF cycles using patients’ own oocytes. All oocytes were fertilized by intracytoplasmic sperm injection (ICSI). Blastocysts underwent trophoctoderm biopsy, and PGT-A was performed using next-generation sequencing (NGS). A total of 750 biopsied blastocysts were analyzed for chromosomal status. Clinical outcomes were evaluated in 1,069 SET cycles, including 594 euploid embryo transfers following PGT-A and 475 morphology-selected embryo transfers without PGT-A. Patients were stratified into five maternal age groups: <35 years (control), 35-37 years, 38-40 years, 41-42 years, and >42 years. The primary outcome was live birth rate, while positive β-hCG rate was evaluated as a secondary outcome.

Results: Embryo aneuploidy increased significantly with advancing maternal age, rising from 22.0% in the control group to 36.0%, 55.9%, 64.5%, and 78.3% across successive age groups (p < 0.001). Positive β-hCG rates remained relatively stable following PGT-A (58%, 56%, 52%, 52%, and 50%), whereas conventional embryo selection showed a progressive decline (56%, 35%, 30%, 29%, and 10%). Live birth rates following PGT-A also remained stable (52%, 49%, 48%, 46%, and 45%), while conventional embryo selection declined from 45% to 16% with increasing maternal age.

Conclusions: Advancing maternal age is associated with a marked increase in embryo aneuploidy and declining reproductive outcomes. PGT-A maintained positive β-hCG and live birth rates across maternal age groups, with the greatest clinical benefit observed in women older than

42 years. These findings support the use of PGT-A as an effective embryo selection strategy for patients of advanced maternal age.

Keywords: advanced maternal age; embryo aneuploidy; IVF; next-generation sequencing; live birth; PGT-A; single embryo transfer.

Declarations

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CARRIER SCREENING: ASSESSING GENETIC RISKS AND PLANNING FOR A HEALTHY FUTURE

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ABSTRACT

Background: Carrier screening is a genetic test used to determine whether an individual carries a pathogenic genetic variant associated with inherited disorders such as cystic fibrosis, spinal muscular atrophy, or sickle cell disease. The test can be performed using a simple blood sample or a buccal (inside-the-cheek) swab. Carrier screening is ideally performed before pregnancy but may also be undertaken during early pregnancy. Identifying carrier status enables couples to assess their reproductive risks and make informed decisions regarding family planning. This study aims to raise patient awareness of the importance of carrier screening and to encourage healthcare professionals to emphasize its role in reproductive care.

Methods: A comparative analysis was conducted using current scientific evidence and clinical experience accumulated at our reproductive center. Contemporary approaches to carrier screening, their clinical applications, and associated outcomes were reviewed and evaluated.

Results: Carrier screening identifies couples at increased risk of having a child affected by inherited genetic disorders. When both partners carry a pathogenic variant for the same autosomal recessive condition, there is a 25% risk that their child will inherit the disease. Early identification allows couples to receive appropriate genetic counselling, plan medical care, consider available reproductive options, and, where appropriate, benefit from advances in reproductive genetics and assisted reproductive technologies. Our clinical experience supports the value of carrier screening as an important component of preconception and early prenatal care.

Conclusions: Carrier screening plays a crucial role in reproductive medicine by enabling early identification of genetic risks and supporting informed reproductive decision-making. Increasing awareness among both patients and healthcare professionals may help prevent inherited disorders and promote healthier future generations. The integration of carrier screening into routine reproductive healthcare should be encouraged as part of comprehensive genetic counselling and ethical medical practice.

Keywords: carrier screening; genetic counselling; genetic testing; inherited disorders; reproductive medicine.

Declarations

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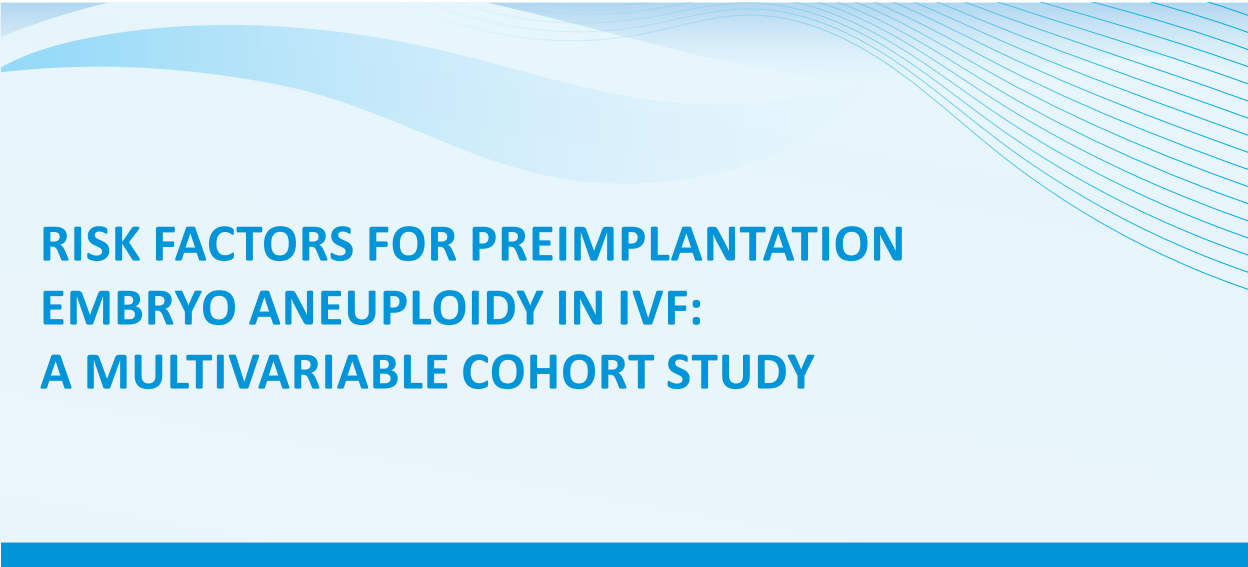
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RISK FACTORS FOR PREIMPLANTATION EMBRYO ANEUPLOIDY IN IVF: A MULTIVARIABLE COHORT STUDY

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ABSTRACT

Background: Embryo aneuploidy remains one of the major unresolved challenges in assisted reproductive technology (ART), significantly reducing embryo implantation potential and overall IVF success. Although the biological mother’s (oocyte provider) age is the primary risk factor for chromosomal abnormalities, additional paternal, ovarian, and embryological factors may also influence embryonic ploidy status. This study evaluated the association between multiple risk factors and embryo aneuploidy in a large cohort of embryos undergoing preimplantation genetic testing for aneuploidy (PGT-A).

Methods: This retrospective cohort study analyzed approximately 6,000 embryos that underwent PGT-A following intracytoplasmic sperm injection (ICSI) at the Georgian-German Reproduction Center between 2025 and 2026. The association between embryo aneuploidy and predefined maternal, paternal, ovarian, and embryological factors was evaluated, including biological mother age, paternal age, anti-Mullerian hormone (AMH) level, ovarian response, blastocyst developmental stage (Day 5 versus Day 6), blastocyst morphology, and paternal infertility diagnosis. Following the initial group-based comparisons, a multivariable logistic regression analysis is being performed to evaluate the independent association between these factors and embryo ploidy status.

Results: Analysis of approximately 6,000 PGT-A-tested embryos demonstrated a euploidy rate of 69%, an aneuploidy rate of 16%, a mosaic embryo rate of 5%, a segmental chromosomal abnormality rate of 7%, and a no-result rate of 2%. During the two-year study period, approximately 960 embryos were classified as aneuploid. Multivariable analysis is ongoing to identify independent predictors of embryo aneuploidy.

Conclusions: Analysis of this large cohort confirms that embryo aneuploidy remains a clinically important challenge in IVF. Identification of independent maternal, paternal, ovarian, and embryological risk factors through multivariable analysis may improve understanding of embryo developmental competence and support more individualized patient counselling and clinical decision-making.

Keywords: aneuploidy; embryo morphology; in vitro fertilization; multivariable analysis; preimplantation genetic testing for aneuploidy.

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GENOME-WIDE PREIMPLANTATION GENETIC TESTING FOR MONOGENIC DISORDERS IN REAL CLINICAL PRACTICE

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ABSTRACT

Background: ESHRE Preimplantation Genetic Testing (PGT) Consortium data from 2012, 2020, and 2023 demonstrate a clear global increase in the utilization of preimplantation genetic testing for aneuploidy (PGT-A), whereas applications of preimplantation genetic testing for monogenic disorders (PGT-M) have remained relatively limited. One major factor contributing to this difference is the technical complexity of conventional PGT-M workflows. Since the 1990s, PGT-M has largely relied on STR-based multiplex nested PCR approaches. Subsequently, the introduction of whole-genome amplification (WGA) for combined PGT applications increased allele dropout (ADO) rates and further complicated laboratory workflows, limiting the broader adoption of PGT-M. In addition, exome- and genome-based analyses increasingly reveal findings involving multiple genes, making conventional single-gene PGT-M strategies more challenging in routine clinical practice.

Methods: A genome-wide SNP-based PGT-M workflow integrated with concurrent PGT-A analysis was implemented in routine clinical practice. The workflow enabled simultaneous testing for monogenic disorders, aneuploidy screening, polyploidy detection, and sibling analysis within a single assay. As the current GenomeScope PGT-M workflow does not directly support mutation analysis, family-specific genotypes were established separately and integrated into the SNP-based haplotyping pipeline. Direct embryo mutation analysis was additionally incorporated to improve diagnostic accuracy and support haplotype reconstruction in non-informative cases.

Results: A total of 10 families, 37 genes, and 132 embryos were analyzed. Compared with conventional STR-based PGT-M, the platform demonstrated a 96% concordance rate. Heterozygous and unaffected embryos represented 76% of all embryos analyzed. Amplification failure, inconclusive results, allele dropout, recombination, and maternal contamination rates were 2.6%, 0.1%, 1.4%, 1.3%, and 0.1%, respectively. The workflow was compatible with the MGI sequencing platform, improving cost efficiency, reducing turnaround time, and simplifying wet-laboratory processes.

Conclusions: Genome-wide PGT-M provides a scalable and clinically practical alternative to conventional STR-based workflows. Beyond single-gene testing, this approach enables comprehensive embryo-level genomic assessment while maintaining high concordance and low technical error rates, supporting broader integration of PGT-M into routine IVF laboratory practice.

Keywords: genome-wide amplification; mutation analysis; preimplantation genetic testing for monogenic disorders; SNP-based PGT-M; STR-based analysis.

Declarations

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Unsal E. Genome-wide preimplantation genetic testing for monogenic disorders in real clinical practice. In: Abstract Book of the 7th International Scientific Conference & Workshop “Infertility 35+.” Tbilisi, Georgia; September 12–13, 2026. Georgian-German Reproduction Center; 2026:80–81. <https://doi.org/10.71419/mtggrc.2026.5>

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SNP-ENHANCED PREIMPLANTATION GENETIC TESTING FOR ANEUPLOIDY: IMPROVING SAFETY AND TRACEABILITY IN COMPLEX IVF WORKFLOWS

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ABSTRACT

Background: Conventional next-generation sequencing (NGS)-based preimplantation genetic testing for aneuploidy (PGT-A) primarily relies on copy-number analysis for the detection of whole-chromosome and segmental aneuploidies. However, copy-number variation (CNV)-based approaches remain limited in distinguishing meiotic and mitotic abnormalities, identifying balanced polyploidies such as triploidy, detecting maternal or external contamination, and verifying embryo identity within complex IVF laboratory workflows.

Methods: Recent advances in genome-wide SNP-based technologies enable the integration of parental haplotyping, allele-frequency analysis, parental intensity ratios, and kinship-based quality control into routine PGT-A workflows. This combined approach extends embryo assessment beyond conventional copy-number interpretation and provides additional biological and analytical information from the same embryo biopsy sample. By combining SNP-supported haplotyping with genome-wide copy-number analysis, meiotic and mitotic aneuploidies can be differentiated more accurately. At the same time, polyploid embryos, uniparental inheritance patterns, maternal contamination, and external DNA contamination can also be identified. In addition, sibling-based SNP clustering and kinship analysis provide a genetic chain-of-custody layer that enables verification of embryo identity and biological consistency among embryos originating from the same cohort, reducing the risk of sample mix-up in high-throughput IVF laboratories.

Results: In validation cohorts including embryos with abnormal fertilization patterns and morphologically normal 2PN embryos showing suspicious copy-number profiles, SNP-augmented PGT-A successfully resolved previously inconclusive findings and identified hidden triploidy and contamination events that were not detectable by conventional CNV-based analysis alone. Heterozygous allele-frequency distributions and third-allele patterns enabled clear distinction between true biological abnormalities and technical artifacts.

Conclusions: This next-generation SNP-augmented PGT-A strategy expands the clinical scope of routine embryo testing beyond conventional aneuploidy screening. By integrating genomic

fingerprinting, ploidy assessment, contamination control, and kinship-based quality assurance into a single workflow, the approach supports safer, more informative, and biologically refined embryo selection in modern IVF practice.

Keywords: genome-wide copy-number analysis; parental haplotyping; ploidy assessment; SNP-augmented PGT-A.

Declarations

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თქვენი სანდო პარტნიორი რეპროდუქციული ჯანმრთელობის ყველა ეტაპზე

RareGene 2017 წლიდან თანამშრომლობს მსოფლიოს წამყვან საერთაშორისო ლაბორატორიებთან. თანამედროვე გენეტიკური ტექნოლოგიების, ზუსტი დიაგნოსტიკისა და სამედიცინო გამოცდილების გაერთიანებით, ჩვენი ლაბორატორია ექიმებსა და პაციენტებს სანდო, დროულ და ინდივიდუალურ საჭიროებებზე მორგებულ გენეტიკურ კვლევებს სთავაზობს.

RareGene-ის ერთ-ერთი განსაკუთრებული მიმართულება რეპროდუქციულ ჯანმრთელობაზე ზრუნვაა. ჩვენ გვჯერა, რომ თითოეული რეპროდუქციული გზა უნიკალურია.

ძირითადი გენეტიკური კვლევები

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უსაფრთხოდ და მაღალი სიზუსტით აფასებს ნაყოფში ქრომოსომული დარღვევების რისკს, მათ შორის მე-13, მე-18 და 21-ე ტრისომიებსა და 200-მდე პათოლოგიას.
- **მეტაბოლურ დაავადებათა გაფართოებული სკრინინგი**
დაბადებისთანავე ჩატარებული ტესტირება ხელს უწყობს იშვიათი დაავადებების დიაგნოსტიკასა და მართვას სიმპტომების გამოვლენამდე.
- **სრული ეგზომის სექვენირება / სრული გენომის სექვენირება**
მაღალი დაფარვის გენეტიკური ანალიზი მემკვიდრეობითი და იშვიათი დაავადებების დიაგნოსტიკისთვის.

Your dedicated partner throughout every stage of reproductive health

Since 2017, RareGene has collaborated with leading international laboratories worldwide. By combining advanced genetic technologies, precision diagnostics, and scientific expertise, our laboratory provides physicians and patients with reliable, timely, and personalized genetic testing tailored to individual needs.

Reproductive health is one of RareGene's core areas of expertise. We believe that every reproductive journey is unique.

Key Genetic Tests

- **Expanded carrier screening**
Analysis of 787 genes for couples planning a family; identifies carriers of inherited conditions.
- **Genetic testing for infertility**
Gene panels for women and men, covering nearly all known genetic causes of infertility.
- **Non-invasive prenatal screening (NIPS)**
Safely assesses fetal chromosomal risk with high accuracy, including trisomies 13, 18 and 21 and up to 200 chromosomal conditions.
- **Expanded metabolic screening**
Testing from birth supports the diagnosis and management of rare disorders before symptoms appear.
- **Whole Exome Sequencing / Whole Genome Sequencing**
High-depth genetic analysis for the diagnosis of inherited and rare diseases.

გენეტიკური ინფორმაცია მხოლოდ ლაბორატორიული პასუხი არ არის - ეს არის ცოდნა, რომელიც ოჯახებს საკუთარი და მომავალი თაობების ჯანმრთელობაზე ზრუნვაში ეხმარება.

Genetic information is more than just a laboratory result - it is knowledge that helps families care for their own health and the health of future generations.



FULGENT GENETICS

ფულჯენტი 2011 წელს დაარსდა და დღეს გენომური კვლევების სფეროში ერთ-ერთ წამყვან კომპანიას წარმოადგენს. მისი საქმიანობა ინოვაციურ ტექნოლოგიურ პლატფორმას ეფუძნება.

კომპანია პაციენტებზე ზრუნვის გაუმჯობესებას ემსახურება ონკოლოგიის, პათოლოგიური ანატომიის, ინფექციური და იშვიათი დაავადებების, ასევე რეპროდუქციული ჯანმრთელობის მიმართულებებით. გენეტიკური კვლევების ფართო და მოქნილი პორტფოლიო, მაღალი ხარისხის მომსახურებასთან ერთად, ექიმებსა და პაციენტებს ზუსტი და სანდო დიაგნოსტიკური გადანაცვლებების მიღებაში ეხმარება.

ფულჯენტი პირველი კლინიკური ლაბორატორი იყო აშშ-ში, რომელმაც ახალი თაობის სექვენირების ტექნოლოგიის (NGS) გამოყენებით გენომში ასლების რაოდენობის ცვლილებების (CNV) გამოვლენა დაწერა. დღეს კომპანია გთავაზობთ 18 000-ზე მეტ მონოგენურ ტესტს, 900-ზე მეტ იშვიათი დაავადების პანელს, სრული გენომის სექვენირებას, CNV ანალიზს, მიტოქონდრიული გენომის სექვენირებასა და CLIA/CAP-ის სტანდარტების შესაბამის სექვენირების სერვისებს.

Fulgent ასევე ქმნის სხვადასხვა ტიპის სიმსივნის სამკურნალო ინოვაციურ პრეპარატებს, ნანოკაფსულაციისა და მიზნობრივი თერაპიის თანამედროვე პლატფორმების გამოყენებით. კომპანიის მიზანია, სხვადასხვა სფეროში დაგროვილი გამოცდილების გაერთიანებით, ჩამოყალიბდეს ზუსტი მედიცინის სრულად ინტეგრირებულ კომპანიად.

ფულჯენტი აერთიანებს აშშ-ში მდებარე შვიდ ლაბორატორიას, სადაც ყველა ნიმუშისა და გენეტიკური მონაცემების ანალიზი მკაცრი რეგულაციების დაცვით ხორციელდება.

რეპროდუქციული გენეტიკა Fulgent Genetics რეპროდუქციული გენეტიკის მიმართულებით სრულყოფილ დიაგნოსტიკურ პორტფოლიოს სთავაზობს ექიმებსა და პაციენტებს. კომპანიის კვლევები მოიცავს ოჯახის დაგეგმვის, უნაყოფობის, პრენატალური და პოსტნატალური გენეტიკური დიაგნოსტიკის ყველა ძირითად მიმართულებას. Fulgent-ის მტარებლობის გაფართოებული სკრინინგის პანელი მოიცავს 1 000-ზე მეტ გენს, რაც წყვილებს საშუალებას აძლევს შეაფასონ მემკვიდრეობითი დაავადებების რისკი ოჯახის დაგეგმვის ეტაპზე და მიიღონ ინფორმირებული რეპროდუქციული გადანაცვლებები.

Founded in 2011, Fulgent has evolved into a premier, full-service genomic testing company built around a foundational technology platform.

The company is dedicated to improving patient care across oncology, anatomic pathology, infectious, rare diseases, and reproductive health. Through its broad and flexible portfolio of genetic testing services, combined with high-quality support, Fulgent helps clinicians and patients make accurate and reliable diagnostic decisions.

Fulgent Genetics was the first clinical laboratory in the United States to introduce copy number variation (CNV) detection using next-generation sequencing (NGS) technology. Today, the company offers more than 18,000 single-gene tests, over 900 rare disease panels, whole genome sequencing, whole genome CNV analysis, mitochondrial genome sequencing, and CLIA/CAP quality sequencing services.

Fulgent is developing innovative drug candidates for a broad range of cancers using advanced nanoencapsulation and targeted therapy platforms. By integrating its expertise across multiple disciplines, the company aims to become a fully integrated precision medicine company.

Fulgent operates seven CLIA-certified and CAP-accredited laboratories across the United States, where all patient specimens are processed, while all genomic data are analyzed on secure private servers.

REPRODUCTIVE GENETICS Fulgent Genetics offers a comprehensive reproductive genetics portfolio for physicians and patients. The company's testing portfolio covers all major areas of reproductive genetic diagnostics, including preconception planning, infertility, prenatal, and postnatal genetic testing. Fulgent's **Expanded Carrier Screening** panel includes **more than 1,000 genes**, enabling couples to assess the risk of inherited genetic disorders before pregnancy and make informed reproductive decisions.

Customized Testing for All Tests can be tailored to the unique needs of you and your patients.	CAP/CLIA/CE-IVDR/ISO Certified Industry accreditation and leading technology ensure accurate results.	Expert-led Our genomic panels and proprietary pipelines are built by leaders in the field.	Our Customer Service We pride ourselves on our exceptional service and strong relationships.
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THE ROLE OF IMMUNOLOGICAL FACTORS IN RECURRENT IMPLANTATION FAILURE (RIF) IN IVF PRACTICE

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¹ Georgian-German Reproduction Center, Tbilisi, Georgia

ABSTRACT

Background: Despite the advancement of Assisted Reproductive Technologies (IVF), achieving pregnancy sometimes fails even after multiple high-quality embryo transfers. Recurrent implantation failure (RIF) and recurrent pregnancy loss are manifestations of different stages of the same pathological process. Successful implantation requires the establishment of immune tolerance and a “synchronous dialogue” between the mother and the embryo. The balance of the immune system plays a critical role in this process; an impaired Th1/Th2 ratio, Treg cell deficiency, hyperactivation of uterine (uNK) and peripheral (pNK) NK cells, and elevated pro-inflammatory cytokines are considered the primary immunological causes of implantation failure.

Methods: Modern scientific literature, systematic reviews, meta-analyses, and multicenter studies were reviewed and analyzed regarding:
Quantitative and functional dynamics of the endometrial leukocyte profile, uNK, and pNK cells (evaluated by flow cytometry and immunohistochemistry methods).
Prediction of immunological risk factors for RIF using a Deep Learning model (based on data from 2,463 patients).
Evaluation of the efficacy and safety of immunotherapeutic approaches (glucocorticoids, IVIG, tacrolimus, cyclosporine, intralipids, lymphocyte immunotherapy).

Results: Changes in Immune Markers: In patients with RIF, an increase in the Th1/Th2 ratio, Th17 cell levels, and CD56+16+ cell cytotoxicity is confirmed, along with enhanced synthesis of pro-inflammatory cytokines (IFN- γ , TNF- α) and reduced protective function of Treg cells.

Predictive Model: The Deep Learning model (with 87.4% accuracy) identified the following main immunological and clinical features of RIF: age, Th1/Th2 ratio, BMI, Anti-TPO, ANA, anti-dsDNA, Anti-TTG, CD56, CD16, and anticardiolipin antibodies.

Conclusion: Patients experiencing recurrent IVF failure and implantation loss require in-depth and comprehensive immunological investigation. The data obtained enable the development

of pathogenetically sound, targeted treatment strategies that significantly increase the likelihood of achieving the ultimate desired outcome – a healthy live birth.

Keywords: implantation; immunological aspects; immunotherapy; in Vitro Fertilization (IVF); natural killer (NK) cells (uNK, pNK); recurrent implantation failure (RIF); Th1/Th2 ratio.

Declarations

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Conflict of Interest: The authors declare no competing interests.

CITATION

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EFFICACY OF LYMPHOCYTE IMMUNOTHERAPY IN IMMUNE-MEDIATED INFERTILITY ASSOCIATED WITH ANTISPERM AND ANTIOVARIAN ANTIBODIES

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¹ *I. Zhordania Institute of Human Reproduction, Tbilisi, Georgia*

ABSTRACT

Background: Immune-mediated infertility, involving autoimmune factors such as antiphospholipid, antinuclear, antiovarian, and antisperm antibodies, along with alloimmune mechanisms including impaired recognition of paternal alloantigens and elevated natural killer cell activity, accounts for a significant proportion of unexplained infertility cases. Conventional therapies, including corticosteroids, plasmapheresis, and vitamin therapy, show limited efficacy, highlighting the need for pathogenetically targeted approaches such as paternal lymphocyte immunotherapy (LIT).

Methods: Forty-two women with confirmed immune-mediated infertility, following exclusion of anatomical, genetic, and infectious causes, were treated with purified paternal lymphocytes at the I. Zhordania Institute of Reproductology, Tbilisi, Georgia, from 2008 onward. Thirty-one patients had primary infertility, and 11 had secondary infertility; all had previously failed conventional treatment. Lymphocyte immunization was administered subcutaneously on an out-patient basis, with the number of sessions individualized per patient.

Results: Pregnancy occurred in 21 of 31 patients with primary infertility (68%), following an average of 1.8 immunizations, and in 9 of 11 patients with secondary infertility (81%), following an average of 1.2 immunizations. No procedure-related complications were reported, and children born following treatment showed normal development.

Conclusion: Lymphocyte immunotherapy achieved a favorable clinical response in the majority of treated patients and may serve as a valuable adjunctive method in managing immune-mediated infertility, both independently and alongside assisted reproductive technologies. Further studies are needed to standardize patient selection criteria and immunization protocols.

Keywords: antiovarian antibodies; antisperm antibodies; assisted reproductive technology; immune-mediated infertility; lymphocyte immunotherapy; paternal antigen immunization.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no competing interests.

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OPTIMIZATION OF DIAGNOSTIC EVALUATION AND TREATMENT STRATEGIES FOR IMMUNOLOGICAL FACTORS IN PATIENTS WITH RECURRENT IN VITRO FERTILIZATION FAILURE

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ABSTRACT

Background: Recurrent implantation failure (RIF) is one of the most challenging complications of assisted reproductive technologies (ART), affecting approximately 10-15% of women of reproductive age. Recent studies have demonstrated that implantation failure is determined not only by embryo quality but also by the endometrial immunological microenvironment and disturbances in maternal-fetal immune tolerance. Hyperactivity of uterine natural killer (uNK) cells, a reduction in regulatory T (Treg) cells, disruption of the M1/M2 macrophage balance, functional alterations of dendritic cells, cytokine imbalance, and impaired HLA/KIR interactions are considered the principal immunological mechanisms underlying recurrent implantation failure. This study aimed to optimize diagnostic evaluation and treatment strategies for immunological factors in patients with recurrent in vitro fertilization (IVF) failure through individualized immunological assessment.

Methods: A systematic review of 17 published studies on reproductive immunology was conducted to evaluate diagnostic approaches, immunological assessments, and therapeutic strategies for immunologically mediated recurrent implantation failure. In addition, a clinical observational study involving 21 patients with recurrent implantation failure, no anatomical or endocrine abnormalities, and planned transfer of genetically normal embryos was conducted. Serum interferon-gamma (IFN- γ) and interleukin-4 (IL-4) levels were measured by flow cytometry. Individualized treatment strategies were selected according to each patient's immunological profile.

Results: Among the 21 patients, elevated IL-4 levels were observed in 19.0%, elevated IFN- γ levels in 24.8%, decreased IFN- γ levels in 33.3%, decreased IL-4 levels in 14.3%, and simultaneous elevation of both cytokines in 9.5%. Patients with elevated pro-inflammatory cytokine levels received 20% intralipid infusion, tacrolimus (2-3 mg/day), and macrophage-targeted therapy. Patients with decreased cytokine levels received intravenous immunoglobulin (IVIG) and beta-glucan preparations. Following embryo transfer, clinical pregnancy was achieved in 14 patients, spontaneous pregnancy occurred in 3 patients, and 4 patients proceeded to the next

embryo transfer cycle. These findings suggest that individualized treatment based on immunological profiling may improve implantation outcomes. However, the limited sample size requires confirmation of these findings in larger randomized clinical studies.

Conclusions: Immunological factors are among the major etiological components of recurrent implantation failure. Hyperactivity of uterine natural killer cells, disruption of the M1/M2 macrophage balance, functional alterations of dendritic cells, reduction of regulatory T cells, and cytokine imbalance may adversely affect the implantation process. Modern reproductive immunology increasingly supports individualized diagnostic evaluation and targeted immunotherapy based on each patient’s immunological profile rather than the routine application of standardized treatment protocols.

Keywords: cytokines; immunotherapy; in vitro fertilization; recurrent implantation failure; reproductive immunology; regulatory T cells; uterine macrophages; uterine natural killer cells.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no competing interests.

CITATION

Sultanova G. Optimization of diagnostic evaluation and treatment strategies for immunological factors in patients with recurrent in vitro fertilization failure. In: Abstract Book of the 7th International Scientific Conference & Workshop “Infertility 35+.” Tbilisi, Georgia; September 12–13, 2026. Georgian-German Reproduction Center; 2026:89–90. <https://doi.org/10.71419/mtggrc.2026.5>

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Invited Review Lecture

CONTRACEPTION IN WOMEN AGED 35+

MARTIN BIRKHAUSER, MD, Professor Emeritus

Gynaecological Endocrinology and Reproductive Medicine, University of Bern, Bern, Switzerland

ABSTRACT

Healthy, non-obese, non-smoking women older than 35 years without personal contraindications may use all hormonal and non-hormonal contraceptive methods until the natural age of menopause. However, the prevalence of cardiovascular and metabolic risk factors increases with age, and underlying medical conditions or an unfavorable lifestyle may substantially influence contraceptive choice. Vascular risk is potentiated by increasing age, obesity, smoking, arterial hypertension, and diabetes mellitus. The presence of any arterial disease constitutes an absolute contraindication to combined hormonal contraception (CHC). Among contraceptive methods considered safe for healthy young women, CHC carries the highest risk of serious complications in women with underlying medical conditions. In contrast, copper intrauterine devices (Cu-IUDs) are associated with the lowest vascular risk. Hormonal alternatives to CHC include progestin-only contraceptives, including the levonorgestrel-releasing intrauterine device. When no further pregnancies are desired, sterilization of either partner represents an effective permanent contraceptive option. Because of their comparatively low contraceptive efficacy, barrier methods used alone and natural family planning should be strongly discouraged in women with significant underlying disease, as unintended pregnancy may present substantial risks for both the mother and the fetus.

Whenever relevant comorbidities are present, consultation with the treating specialist is recommended before initiating hormonal contraception. Regardless of the contraceptive method selected, women at risk of sexually transmitted infections should also use an appropriate barrier method for protection against infection.

Keywords: combined hormonal contraception; obesity; perimenopause; smoking; vascular risk.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no competing interests.

CITATION

Birkhauser M. Contraception in women aged 35+. In: Abstract Book of the 7th International Scientific Conference & Workshop "Infertility 35+." Invited review lecture. Tbilisi, Georgia; September 12–13, 2026. Georgian-German Reproduction Center; 2026:91. <https://doi.org/10.71419/mtggrc.2026.5>

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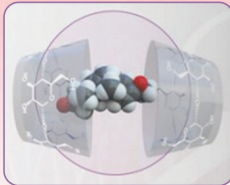
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პლემირისი

პროგესტერონი 25მგ

პროგესტერონის წყალხსნარი
კანქვეშა გამოყენებისთვის

ორიგინალური ფორმულის წყალხსნარი არ შეიცავს კონსერვანტებს და
გამხსნალებს, რაც განაპირობებს მინიმალურ ალერგიულ თუ ადგილობრივ
ქსოვილოვან რეაქციებს, რაც შეიძლება თან ახლდეს პროგესტერონის
ზეთოვანი ხსნარის გამოყენებას



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გამოყენებისთვის

დოზირება ექიმის რეკომენდაციით

მწარმოებელი:
Laboratorios Leon Farma. ესპანეთი

ცხოვრება მშვენიერად

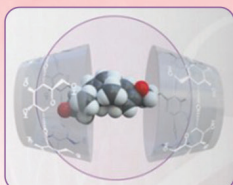


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ADENOMYOSIS AND REPRODUCTIVE DYSFUNCTION: CURRENT APPROACHES

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ABSTRACT

Background: Adenomyosis is a benign uterine pathology increasingly associated with infertility, recurrent pregnancy loss, and adverse pregnancy outcomes. This review examines current approaches to the diagnosis and management of adenomyosis in women with impaired reproductive function.

Methods: The study included 155 patients aged 18-45 years with benign uterine pathologies and reproductive dysfunction. The patients were divided into four groups: Group I, women with adenomyosis (19 patients); Group II, women with endometrial hyperplasia (43 patients); Group III, women with uterine fibroids (68 patients); and Group IV, women with endometrial polyps (25 patients).

Results: The clinical presentation was variable and included dysmenorrhea (73.7%), abnormal uterine bleeding (57.9%), chronic pelvic pain (31.3%), and infertility, including primary infertility (21.1%) and secondary infertility (36.8%). Spontaneous early miscarriages were observed in 47.4% of patients, and recurrent miscarriages in 36.8%. Estradiol, follicle-stimulating hormone (FSH), and prolactin levels were higher in the adenomyosis group than in the other groups. Uterine artery Doppler assessment demonstrated significantly higher systolic/diastolic (S/D) ratio, resistance index (RI), and pulsatility index (PI) values in patients with adenomyosis compared with those with other benign uterine pathologies.

Conclusions: Current approaches include medical therapy, assisted reproductive technologies, and, in selected cases, fertility-preserving surgery. Timely diagnosis and a personalized treatment strategy may help improve fertility potential and pregnancy outcomes.

Keywords: adenomyosis; assisted reproductive technologies; benign uterine pathologies; infertility; miscarriage; reproductive dysfunction.

Declarations

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FERTILITY IN INDIVIDUALS WITH DIFFERENCES/DISORDERS OF SEX DEVELOPMENT

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ABSTRACT

Background: Infertility is one of the most common consequences of differences/disorders of sex development (DSD) and has a substantial impact on quality of life. Fertility potential varies considerably according to the underlying DSD diagnosis. Advances in assisted reproductive technologies (ART) have dramatically expanded reproductive options for individuals with DSD, enabling parenthood in clinical situations that were previously considered incompatible with fertility. This review summarizes current fertility options for individuals with DSD and discusses recent advances in reproductive medicine and fertility preservation.

Methods: A narrative review of the current literature was combined with the authors' clinical experience in managing individuals with DSD. Fertility outcomes were analyzed across different DSD conditions, including sex chromosome abnormalities, disorders of gonadal development, androgen insensitivity syndrome, and Mullerian anomalies. Current reproductive strategies, including oocyte and sperm donation, fertility preservation, microdissection testicular sperm extraction (micro-TESE), platelet-rich plasma (PRP) therapy, stem cell-based regenerative approaches, gestational surrogacy, and assisted reproductive technologies, were reviewed. Clinical examples from the authors' practice included three women with mosaic Turner syndrome (45, X/46, XX) who achieved pregnancy and live birth through oocyte donation, five women with Mullerian agenesis who became genetic mothers through gestational surrogacy, and 280 women with septate or T-shaped uterus in whom hysteroscopic correction resulted in successful term pregnancy and live birth in 74-85% of cases. The review also highlights encouraging reproductive outcomes in selected patients with partial androgen insensitivity syndrome and in individuals with Swyer syndrome following appropriate endocrine management and the use of donor oocytes.

Conclusions: Differences/disorders of sex development should not be regarded as synonymous with absolute infertility. Fertility potential varies considerably among different DSD conditions,

making early diagnosis, individualized reproductive counselling, and appropriate fertility preservation strategies essential. Advances in assisted reproductive technologies have made biological parenthood possible in many situations that were previously considered untreatable. Optimal reproductive care requires a personalized, multidisciplinary approach involving clinical geneticists, endocrinologists, reproductive medicine specialists, psychologists, and specialized surgeons.

Keywords: androgen insensitivity syndrome; assisted reproductive technology; differences/disorders of sex development; fertility preservation; infertility; Klinefelter syndrome; Mullerian anomalies; Swyer syndrome; Turner syndrome.

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ESTROBOLOME: A NEW FRONTIER IN WOMEN'S HEALTH AFTER THE AGE OF 35

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ABSTRACT

Background: Obesity, insulin resistance, metabolic dysfunction, and binge eating disorder (BED) become increasingly prevalent in women after the age of 35. This period is characterized by progressive hormonal changes, alterations in body composition, shifts in appetite regulation, and an increased susceptibility to weight gain. Emerging evidence suggests that the gut microbiota and estrogen metabolism are interconnected through the estrobolome, forming a bidirectional gut-estrogen-brain axis that may influence eating behavior, energy homeostasis, and metabolic health. This review proposes a novel conceptual framework linking the estrobolome and the gut-estrogen-brain axis to obesity, binge eating behavior, and metabolic dysfunction in women over 35 years of age.

Methods: A narrative review of contemporary scientific literature was conducted, focusing on gut microbiota composition, estrogen metabolism, appetite-regulating hormones, neuroendocrine pathways, eating behavior, and metabolic health in adult women. Particular attention was given to studies investigating the estrobolome, gut-brain communication, and hormonal changes associated with the perimenopausal transition.

Results: Current evidence indicates that gut microbiota dysbiosis may alter the production of microbial metabolites and influence the secretion of key appetite-regulating mediators, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and serotonin. Simultaneously, alterations in estrogen bioavailability may affect hypothalamic satiety signaling and dopaminergic reward pathways, contributing to food cravings, emotional eating, and binge eating behavior. The estrobolome appears to play a central role in regulating estrogen recirculation and bioavailability, potentially linking microbiota composition with hormonal and metabolic regulation. These interactions may contribute to obesity, insulin resistance, visceral adiposity, and behavioral eating disturbances in women after the age of 35.

Conclusions: The gut-estrogen-brain axis represents a promising conceptual framework for understanding obesity, binge eating behavior, and metabolic dysfunction in women over the age of 35. Although causality remains to be fully established, growing evidence supports a signif-

icant interaction between gut microbiota and estrogen metabolism. The estrobolome may represent a previously underrecognized regulator of metabolic and behavioral health in women after the age of 35, opening new opportunities for personalized prevention and treatment strategies.

Keywords: binge eating disorder; estrogen; estrobolome; gut-estrogen-brain axis; metabolic health; microbiota; obesity; perimenopause; women's health.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Tbilisi, Georgia

Research Article

ARTIFICIAL INTELLIGENCE
IN EMBRYO SELECTION
WHAT EVERY REPRODUCTIVE
SPECIALIST SHOULD KNOW

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ABSTRACT

Background: Artificial intelligence (AI) is rapidly becoming an important component of modern in vitro fertilization (IVF), offering opportunities to standardize embryo assessment, reduce subjectivity, and efficiently analyze static and time-lapse imaging data.

Methods: A focused narrative review synthesized 17 publications from 2021 through 2025 on AI-assisted embryo ranking, viability and euploidy prediction, workflow optimization, quality assurance, and implementation: 1 randomized clinical trial, 1 systematic review, 2 conference abstracts, and 13 other journal publications. Four named embryo-assessment systems were profiled. Separately, published aggregate GGRC data were synthesized to illustrate a practice-based application of AI in IVF laboratory quality management.

Results: ERICA, iDAScore, FiTTE, and IVFvision. ai provided automated embryo ranking or outcome prediction. Most supporting evidence was retrospective or simulation-based. In the only included multicenter randomized trial (n = 1,066), iDAScore did not establish noninferiority to standard morphology-based selection for clinical pregnancy; however, embryo assessment was approximately tenfold faster. The GGRC evidence demonstrated a complementary quality-management application rather than image-based embryo ranking: a KPI-based clinical pregnancy model was externally validated using 3,888 Georgian treatment cycles within a two-center dataset of 10,128 cycles, yielding a mean AUC of 0.73. In Q2 2024, predicted and observed clinical pregnancy rates were 58.9% and 59.1%, and no statistically significant between-embryologist differences were detected. These findings support AI-assisted calibration and laboratory audit but do not demonstrate improved pregnancy or live-birth outcomes.

Conclusion: AI’s strongest current contribution is human-supervised decision support and laboratory governance. The GGRC experience demonstrates practical value for calibration, KPI surveillance, troubleshooting, and targeted audits, but it does not yet prove that AI increases pregnancy or live-birth rates. Thoughtfully implemented AI can strengthen standardization,

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workflow, training, quality control, and evidence-based IVF care. However, it should not replace embryologists or be presented as a guarantee of euploidy, pregnancy, or live birth.

Keywords: artificial intelligence; embryo selection; IVF; time-lapse imaging; machine learning; deep learning; euploidy; reproductive medicine

Introduction

Embryo selection is central to IVF because clinicians aim to identify the embryo most likely to implant while supporting safe single-embryo transfer.¹ Morphology remains the clinical benchmark: it is inexpensive, familiar, and biologically meaningful.¹ Yet it is also subjective, depends on observer experience, and is usually based on a limited number of static observations.² AI became relevant as time-lapse incubators and digital imaging generated more data than can be reviewed efficiently by manual methods alone.^{3,4} Machine-learning systems can apply the same scoring rules repeatedly and may recognize complex visual or developmental patterns that are difficult to detect consistently by human observers.²⁻⁴ Figure 1 shows the main reasons for using AI in embryo assessment.

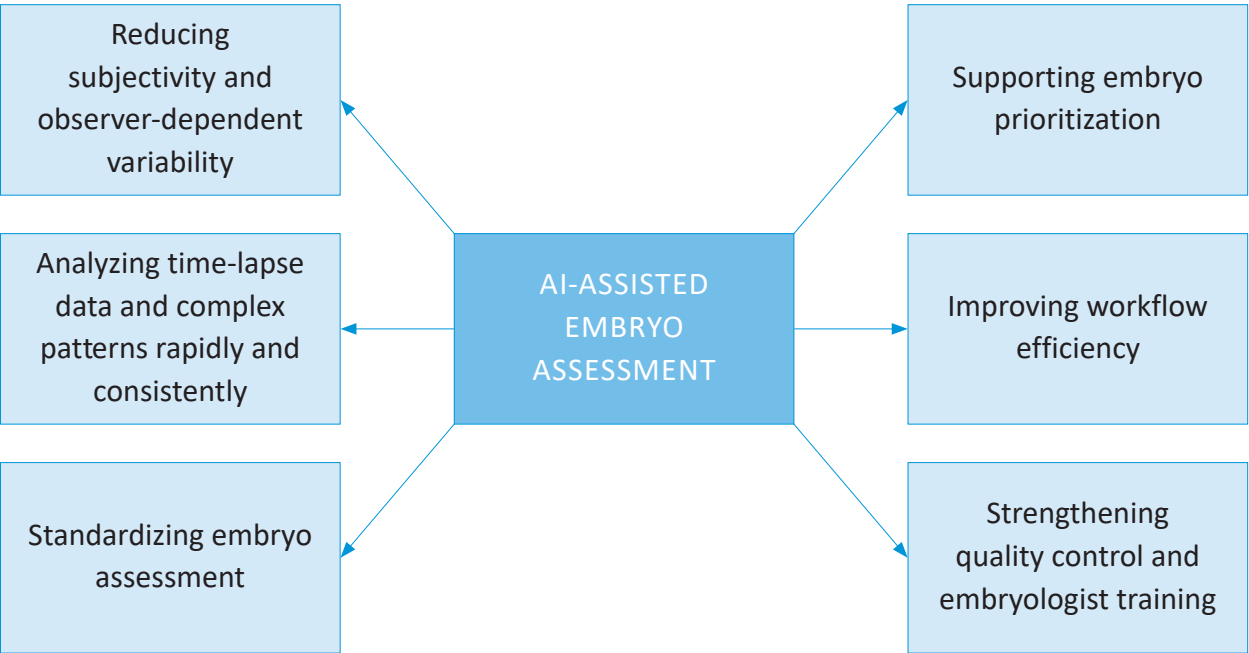


Figure 1. The clinical drivers for AI adoption in embryo assessment.

Three messages for reproductive specialists

- **Why AI is relevant:** IVF laboratories need greater consistency, faster review, and better use of image-rich data.
- **What AI can do today:** support embryo ranking, workflow optimization, standardization, training, and quality control.
- **What AI cannot yet do:** replace the embryologist, guarantee euploidy, or prove an increase in live birth across routine practice.

Methods

A focused narrative review was conducted in PubMed and Google Scholar for English-language publications on AI-assisted embryo ranking, viability and euploidy prediction, workflow opti-

zation, quality assurance, and implementation, dated January 1, 2021, through December 31, 2025. Seventeen publications were included in the qualitative synthesis: 1 randomized clinical trial, 1 systematic review, 2 conference abstracts, and 13 other journal publications. Multi-center and multi-clinic evidence was retained within these design categories. Four named embryo-assessment systems – ERICA, iDAScore, FiTTE, and IVFvision. ai – were profiled. Separately, published aggregate GGRC data were synthesized to illustrate a practice-based application of AI in IVF laboratory quality management.

Search concepts combined “artificial intelligence” or “machine learning” with “embryo selection”, “embryo ranking”, “time-lapse”, “blastocyst”, “euploidy”, “implantation”, “clinical pregnancy”, “IVF”, or “laboratory KPI. ” Eligible reports involved human IVF and provided a clinically or operationally interpretable outcome, including embryo ranking, viability or euploidy prediction, implantation or pregnancy prediction, assessment time, external validation, laboratory quality control, or staff-performance monitoring. Animal-only studies, publications outside the date or language limits, and purely technical studies without a clinically interpretable outcome were excluded. Conference abstracts were retained as preliminary evidence and interpreted cautiously.

Data extraction included study design, sample size, clinical setting, model inputs, comparator, target outcome, validation approach, performance metrics, and reported limitations. Evidence was weighted according to study design and validation strength. Randomized prospective evidence was given the greatest weight in assessing clinical effectiveness, while the systematic review was used to contextualize the broader evidence base. Multicenter studies and independent external validation informed the assessment of generalizability, whereas single-center retrospective studies and conference abstracts were regarded as preliminary evidence. Because the included studies differed substantially in model architecture, input data, comparators, outcome definitions, and clinical endpoints, quantitative pooling was considered inappropriate; findings were therefore synthesized narratively.

The practice-based GGRC component synthesized previously published aggregate data reported by Sergeev et al, including laboratory KPIs, model calibration over time, observed versus predicted clinical pregnancy rates, staff-level comparisons, discordant-case analysis, and documented quality-management actions.^{11,16,17} No new patient-level analyses or statistical re-analyses were conducted. Because the published GGRC reports did not include a controlled preimplementation comparison, temporal changes were interpreted as changes in prediction-outcome agreement and model calibration – not as evidence that AI increased clinical pregnancy or live-birth rates or reduced variability between embryologists.¹¹

Results

Why AI Became Necessary in Embryology

Conventional morphology captures important features, but embryo grading can vary among embryologists and even within the same observer over time.^{1,2} This variability becomes more important in high-volume laboratories, multicenter networks, and situations in which several embryos appear morphologically similar.^{2,5}

Time-lapse imaging introduced continuous monitoring of embryo development, allowing detailed assessment of key morphokinetic events, including pronuclei appearance and fading (tPNa and tPNf), cleavage timings (t2-t8), morula compaction (tM), the start of blastulation (tSB), blastocyst expansion, cell-cycle progression, and developmental synchronization.³ These

recordings are clinically valuable but time-consuming to annotate manually.³ Automated analysis can process thousands of images efficiently and convert complex developmental data into reproducible scores or standardized developmental profiles.^{3,4} Importantly, AI does not improve the intrinsic quality of an embryo.^{1,5} Its role is to prioritize the embryos already available and to make assessment more consistent, efficient, and auditable.^{1,4,5}

How AI Works – Without the Technical Jargon

Machine learning identifies relationships between defined inputs – such as morphology, cleavage timing, maternal age, or laboratory variables – and a known outcome.² Deep learning is a more automated form of machine learning that can learn visual patterns directly from embryo images or image sequences.^{2,4} Static-image systems analyze one or a small number of selected images, whereas time-lapse systems analyze development across multiple time points.^{2,4,6,7} Multimodal systems combine images with clinical or laboratory information.^{6,8} Figure 2 illustrates the simplified workflow of AI-assisted embryo assessment. The output is usually a ranking or probability – for example, predicted viability, implantation potential, or likelihood of euploidy.^{6,8} These outputs support embryo prioritization but should not be interpreted as a diagnosis or guarantee of pregnancy.^{8,9}

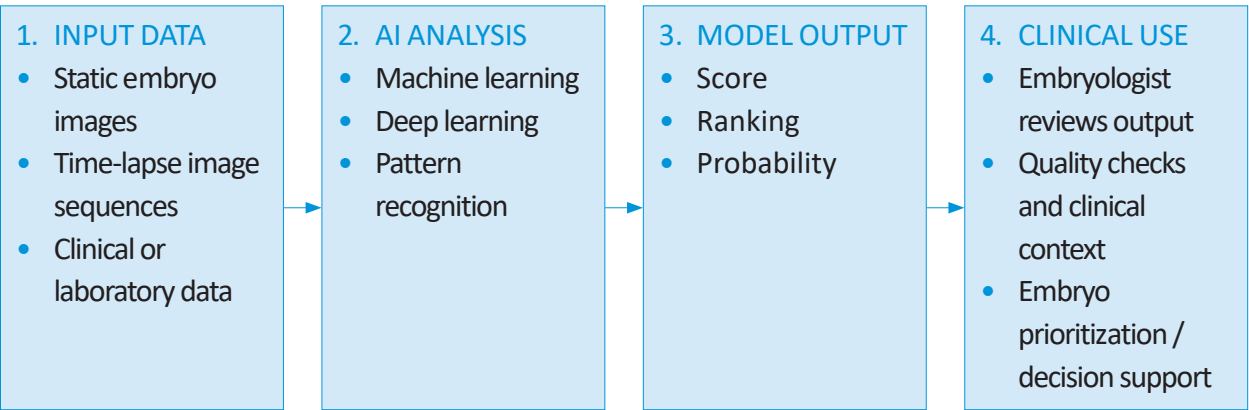


Figure 2. Main data inputs and outputs of AI-assisted embryo assessment models.

AI systems also differ in the transparency of their decision-making processes. Some models function as “black boxes”, producing predictions without clearly showing which features influenced the results.² More interpretable or hybrid systems allow embryologists to examine the morphological, morphokinetic, or clinical variables that contributed to a prediction.² Lee et al classified AI decision-support systems according to their degree of interpretability, as summarized in Table 1.² This distinction is clinically important because greater transparency may improve user trust, quality control, and the embryologists’ ability to understand or question an AI-generated recommendation.

Table 1. Classification of AI Decision-Support Systems for Embryo Selection According to Interpretability.

Category	Annotation Step	Ranking Step	Interpretability
Black-box	None	Black-box methods	Lowest
Matte-box	Manual or automatic	Black-box methods	Moderate
Glass-box	Manual or automatic	Interpretable ML (decision tree, logistic regression, Bayesian network, random forest)	Highest

Adapted by the author from Lee et al.² Abbreviations: ML, machine learning.

Programs Currently Discussed in Clinical Embryology

The available systems differ in their input data, intended outcome, transparency, and evidence base.^{2,4,6,7,10} They should not be treated as interchangeable products.^{2,5} Importantly, not every clinically useful AI system directly ranks embryos. Four embryo-assessment systems are compared in Table 2. The GGRC model is separate because it combines laboratory and clinical KPIs for pregnancy prediction, audit, staff assessment, and quality improvement rather than ranking embryo images.¹¹

What the Evidence Shows

Systematic reviews and retrospective studies generally show that AI can match or outperform individual embryologists on selected image classification or prediction tasks.¹³ AI can markedly reduce annotation time and provide consistent scoring.^{4,12} Automated morphokinetic analysis can identify developmental patterns associated with implantation-related outcomes.³ Promising discrimination does not automatically translate into improved live birth.^{5,8,12,13} Models trained on morphology, implantation, biochemical pregnancy, or euploidy answer different questions. For example, a multimodal model predicted euploidy with good discrimination but did not effectively predict live birth after frozen embryo transfer. 8 Live birth reflects the entire reproductive and obstetric pathway and cannot be inferred from embryo appearance alone.^{8,12,13}

The strongest prospective evidence remains cautious.¹² In a multicenter randomized trial of 1,066 patients, clinical pregnancy occurred in 46.5% of the iDAScore group and 48.2% of the morphology group.¹² The trial did not establish noninferiority using its prespecified margin.¹² However, embryo evaluation was approximately tenfold faster with AI.¹²

Table 2. Selected AI systems and their current clinical interpretation.

System	Primary input	Current purpose and evidence	Practical caution
ERICA	Single static blastocyst image	Ranks embryos using a noninvasive image. ⁷ In a 2025 controlled simulation study, ERICA outperformed participating embryologists in selecting a euploid embryo on the first attempt. ⁷ It can support embryo prioritization, decision-making, and embryologist training. ⁷	Its effect on live-birth outcomes in routine practice has not been established. ^{5,7} Performance depends on image acquisition and workflow integration. ^{5,7}
iDAScore	Time-lapse image sequence	Provides fully automated embryo ranking by analyzing spatial and temporal patterns throughout embryo development. ⁴ A large retrospective multicenter study supported reproducible scoring and demonstrated partial generalizability across previously unseen clinics. ⁴ In a randomized trial, evaluation was about 10-fold faster than with standard morphology assessment. ¹²	The randomized trial did not demonstrate noninferiority for clinical pregnancy compared with standard morphology-based selection. ¹² Therefore, current evidence supports its value for automation, standardization, and workflow efficiency, but does not establish superior pregnancy or live-birth outcomes. ^{5,12}
FITTE	Single static day-5 blastocyst image, optionally combined with clinical variables.	Predicts blastocyst viability and the probability of clinical pregnancy after single-embryo transfer. ⁶ Grad-CAM provides visual explanations of the image regions contributing to the prediction. ⁶ Performance improved when image data were combined with clinical variables, illustrating the potential of multimodal AI. ⁶	Evidence is based on a retrospective, single-center study and requires broader external and prospective validation. ^{5,6} Visual explanations may improve interpretability but do not establish causality or eliminate bias and uncertainty. ^{6,9}
IVFvision.ai	Single static day-5 blastocyst image	Predicts implantation potential. ¹⁰ Preliminary external validation data suggest that image centering and the addition of clinical or laboratory variables, such as fertilization method and KIDScoreD5, can materially affect performance. ¹⁰	Evidence is limited to a retrospective conference abstract based on a small sample of 113 blastocyst images. ¹⁰ Performance was highly dependent on image quality and blastocyst positioning, highlighting the need for standardized image acquisition and larger prospective validation studies. ¹⁰

Table developed by the author based on published evidence.

Practice-Based GGRC Experience: From Clinical Pregnancy Prediction to IVF Quality Management

This practice-based synthesis describes a broader practical application of AI in IVF laboratory management, using published aggregate data from GGRC and related multicenter validation and audit reports; it is not a new patient-level analysis.^{11,16,17} Unlike embryo-ranking tools, this system combines clinical variables and laboratory KPIs to estimate the expected probability of clinical pregnancy. Observed outcomes can then be compared with model-generated predictions for defined patient groups, time periods, and staff members to identify discrepancies requiring quality review.

Data foundation and external validation: The GGRC external validation dataset included 3,888 treatment cycles (2022-2024) and four embryologists. With a second external center, 10,128 total cycles yielded a mean AUC of 0.73.¹⁶ A subsequent GGRC analysis included 665 treatment cycles with embryo-transfer outcomes from 2024.¹⁷ Non-calibrated AUCs across nine other clinics ranged from 0.55 to 0.73, emphasizing the importance of validating and calibrating prediction models for each clinic's patient population and clinical practices.¹⁷

Real laboratory KPIs: In the later GGRC analysis, mean fertilization, blastocyst-development, and total good-quality blastocyst development rates were 0.83 (95% CI, 0.70-0.96), 0.52 (0.48-0.56), and 0.43 (0.37-0.50), respectively, compatible with consensus targets.¹⁷ In the externally validated prediction model, LIME-derived values associated with classification into the positive-pregnancy group included an oocyte-retrieval rate of 0.83, MII rate of 0.78, fertilization rate of 0.64, blastocyst-development rate of 0.44, TGBDR of 0.35, and KPIScore of 17.¹⁶ These are interpretive thresholds for the analyzed datasets and should not be regarded as universal clinical cutoffs or causal requirements for pregnancy.

Model calibration over time: No controlled comparison of clinical outcomes before and after AI implementation was reported. Mean absolute error between predicted and observed aggregate pregnancy rates fell from 0.15 in 2022 Q1 to 0.03 in 2024 Q2 ($p < 0.05$) as data increased and the algorithm was refined. In Q2 2024, following integration of the quality-control system, the predicted clinical pregnancy rate was 58.9%, compared with an observed rate of 59.1%, representing a difference of 0.2 percentage points.¹⁷ These findings demonstrate improved model calibration.

Embryologist consistency and targeted audit. Pairwise comparisons of laboratory KPIs among embryologists in Q2 2024 did not detect statistically significant differences ($p > 0.05$). Among 64 discordant cases identified within 665 transfers, differences associated with the embryologist were also nonsignificant ($p = 0.633$).¹⁷ This supports current consistency. However, nonsignificant findings do not prove equivalence between embryologists, and without a pre-implementation baseline, they cannot demonstrate that variability decreased after AI implementation. Nevertheless, identifying discordant cases provides a practical targeted audit approach: instead of reviewing all cycles equally, the laboratory can focus on further investigating cases in which predicted and observed outcomes differ and assess potential procedural, clinical, data-quality, or model-calibration explanations.¹⁷

Concrete troubleshooting. A 10%-20% decline in 2023 pregnancy probability occurred without significant changes in laboratory KPIs (all $p > 0.05$), redirecting review toward clinical or patient factors. The largest model-outcome discrepancy coincided with 2022 Q2 laboratory reconstruction; that period was excluded.¹¹ Because this was a retrospective observational analysis, it cannot establish the cause of the decline.

Overall, the GGRC experience demonstrates how AI-based clinical-pregnancy prediction can extend beyond individual embryo assessment to support KPI surveillance, model calibration, temporal monitoring, staff-level audit, and structured investigation of unexpected outcomes. Nevertheless, these retrospective findings do not establish that AI independently improves pregnancy or live-birth rates or reduces variability between staff members. Its demonstrated value lies in providing an additional, data-driven component of a human-supervised IVF quality-management system. Table 3 summarizes the principal published GGRC findings and their practical interpretation within an IVF quality-management framework.

Where the Greatest Benefit Is Likely Today

- **Quality control:** calibrated predictions and KPI trends can distinguish a laboratory signal from changes in case mix or clinical practice.
- **Staff development:** case-mix-adjusted audit identified physicians whose observed outcomes were below predicted performance and supported focused supervision and mentoring.¹¹
- **Standardization:** the same algorithm can apply a consistent scoring framework across shifts, operators, and affiliated laboratories.^{2,4,11}
- **High-volume IVF centers:** automated review can reduce time spent on routine ranking and allow experts to focus on complex cases and laboratory oversight.^{4,5,12}

Table 3. Published GGRC Metrics and Their Quality-Management Interpretation.

GGRC measure	Published result	Quality-management interpretation
External validation	3,888 GGRC protocols (2022-2024), evaluated by four embryologists; two-center external validation: 10,128 cycles, mean AUC 0.73. ¹⁶	Supports model generalizability; local validation and calibration remain necessary.
Laboratory KPIs	Fertilization rate 0. 83; blastocyst development rate 0. 52; TGBDR 0.43. ¹¹	Provides real laboratory benchmarks for investigating changes in clinical pregnancy rate.
Model calibration	Quarterly mean absolute error decreased from 0.15 to 0.03 (p < 0.05); predicted vs observed Q2 2024 clinical pregnancy rates were 58.9% and 59.1%. ¹⁷	Demonstrates closer agreement between predicted and observed rates over time; doesn’t show improvement in clinical outcomes.
Embryologist comparison	Pairwise KPI comparisons, p > 0.05; among 64 discordant cases from 665 embryo transfers, differences associated with the embryologist were nonsignificant (p = 0. 633). ¹⁷	No statistically detectable between-embryologist differences were found in the measured analyses; no preimplementation baseline was available to assess whether variability changed.

Practice-based synthesis of published aggregate GGRC data and related validation analyses.^{16,17} Abbreviations: AUC, area under the curve; CI, confidence interval; KPI, key performance indicator; TGBDR, total good-quality blastocyst development rate.

Limitations

Most published studies remain retrospective, and many are based on single-center or selected datasets.^{5,13} Training data may underrepresent difficult embryos, untransferred embryos, certain patient groups, or specific laboratory conditions.^{4,13} Overfitting can produce excellent performance in the development dataset but weaker performance in a new clinic.^{4,5}

External validation is limited, and performance can change with incubator type, image acquisition, culture conditions, transfer policy, patient population, and endpoint definition.^{4,5,10} Small technical issues matter: preliminary IVFvision. ai data showed substantially different performance for centered versus off-centered blastocyst images.¹⁰

Black-box algorithms create problems for trust, counseling, responsibility, and audit.^{9,15} Bias is also possible.^{14,15} A large conference abstract reported small sex-related scoring differences in both manual and some AI methods; the differences were not sufficient for reliable sex selection, but they emphasize the need for subgroup and fairness testing.¹⁴

Cost, software updates, data privacy, licensing, staff training, and performance drift must also be considered.^{5,15} A model should be evaluated not only by accuracy but by whether it fits the laboratory workflow, remains calibrated over time, and produces a measurable clinical or operational benefit.^{5,15}

Discussion

What the GGRC Data Add to Real-World IVF Practice

Most embryo-selection studies ask a narrow question: which embryo should be transferred first? The GGRC program addresses a different operational question: whether the complete clinical-laboratory pathway is performing as expected for defined patient groups and time periods.^{11,16,17} This extends AI beyond single-embryo ranking to an auditable quality-management framework.

Three findings are particularly relevant. Firstly, stable laboratory KPIs during a decline in predicted clinical pregnancy probability help determine that deterioration in laboratory performance is an unlikely explanation. Secondly, closer agreement between predicted and observed pregnancy rates over time demonstrates the practical value of model calibration and continuous performance monitoring. Calibrated predictions reveal staff-level outliers that require supervision. And thirdly, nonsignificant measured differences among embryologists provide reassurance about current consistency. Together, these findings demonstrate practical value for monitoring, troubleshooting, and focused quality review.

A safe workflow begins with technical quality.^{5,10} Poor focus, off-centered blastocyst images, incomplete time-lapse data, or image-acquisition conditions that differ from the model's training data can make an apparently precise score unreliable.^{5,10} The embryologist should perform standard assessment, review the AI result and any available confidence or quality indicators, and investigate clinically important disagreement before making the final decision.^{5,9}

Patients should be told that AI provides an estimate or ranking, not a guarantee.^{5,9,15} Patient counseling should explain what data are used, whether the software is locally validated, and that a high score cannot confirm euploidy or ensure pregnancy and live birth.^{5,8,9,15}

How Clinics Should Implement AI

- Define the intended use before purchase or development: embryo ranking, time-lapse annotation, clinical pregnancy prediction, KPI monitoring, quality control, staff competency assessment, training, or workflow efficiency.

- Record a pre-implementation baseline and validate the system locally against current laboratory practice before allowing it to influence embryo prioritization or staff assessment.
- Measure operational outcomes (assessment time, calibration error, observer variability, detected outliers, and completed corrective actions) alongside clinical outcomes (implantation, clinical pregnancy, miscarriage, and live birth).
- Link alerts and important AI-human disagreements to a documented corrective and preventive action pathway, including review, mentoring when indicated, and repeat audit.
- Reassess model performance after software updates or changes in incubators, laboratory protocols, or patient populations.

Table 4. Current Practical Value and Unproven Claims of AI in Embryo Assessment.

What current evidence supports	What remains unproven	Clinical interpretation
Standardized scoring: Automated systems apply the same scoring method consistently. ^{2,4}	Generalizability remains incompletely demonstrated: some models performed across unseen clinics, whereas many studies lacked external validation or showed site-dependent performance. ^{4,5,10,13}	Validate performance locally and monitor it over time.
Faster assessment: iDAScore evaluation was almost 10 times faster than manual morphology assessment. ¹²	The randomized trial did not establish noninferiority for clinical pregnancy or show improved live birth. ¹²	Workflow efficiency is a valid benefit, even without better clinical outcomes.
Euploidy estimation: A multimodal model combining embryo and clinical data showed good discrimination for euploidy. ⁸	AI cannot confirm chromosomal status and did not reliably predict live birth after euploid embryo transfer. ⁸	Treat the result as a probability estimate, not a diagnosis or substitute for PGT-A.
Embryo prioritization: iDAScore supported implantation-related ranking, while ERICA selected a euploid embryo first more often than embryologists in a simulated task. ^{4,7}	ERICA was evaluated in a simulation, not an embryo-transfer trial. After viewing ERICA rankings, embryologists’ final selections did not improve significantly. ⁷	Use AI as decision support, not as a replacement for expert assessment.
Laboratory audit and staff benchmarking: KPI-based analysis identified differences in staff performance across clinics and supported targeted review. ¹¹	Improved long-term competency, pregnancy rates, or live-birth outcomes after mentoring were not demonstrated. ¹¹	Use AI as a quality-management tool with predefined KPIs and follow-up evaluation.
Training and feedback: AI can provide a consistent benchmark for structured review of discordant cases. ^{7,11}	A sustained improvement in embryologist accuracy or competency has not been established. ⁷	Training value is promising but should be seen as potential rather than proven.

Table developed by the author based on published evidence.

Future Priorities

Future research should prioritize prospective multicenter trials with live birth, cumulative live birth per oocyte retrieval, time to pregnancy, miscarriage, obstetric and neonatal outcomes, cost-effectiveness, and patient experience.^{5,12,15}

Interpretability and fairness should be built into validation rather than treated as optional additions.^{9,14,15} Multimodal systems may ultimately be more useful than image-only models, but they will require larger datasets, stronger privacy protections, calibration, and ongoing surveillance.^{5,6,8,9,15}

Conclusion

Artificial intelligence is no longer only a future concept in embryology; it is already increasingly being evaluated and introduced into IVF practice.^{5,11,12} Its greatest value today lies not in replacing embryologists, but in supporting standardized, reproducible, and evidence-based embryo assessment, workflow efficiency, and laboratory quality management.^{2,5,11,12}

Across 17 included publications, the clearest benefits of AI are standardized scoring, faster assessment, structured embryo ranking, model calibration, and laboratory audit. Superiority for clinical pregnancy or live birth has not been established.^{4,5,12,13,17} The GGRC program provides a concrete practice-based example through a validation cohort of 3,888 treatment cycles, center-specific laboratory KPIs, close agreement between predicted and observed pregnancy rates, and targeted analysis of discordant cases.^{11,16,17} Responsible implementation requires human-supervised AI that is validated locally, monitored continuously, linked to documented review and corrective action paths, and communicated transparently to patients.^{5,9,15,17}

Declarations

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Conflict of Interest: The authors declare no competing interests.

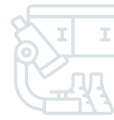
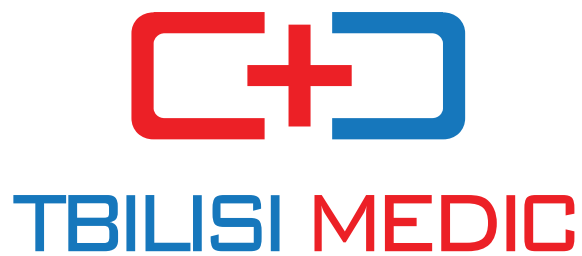
Acknowledgments: The authors have no acknowledgments to declare.

Data Availability: No new patient-level dataset was generated or analyzed. The literature review and practice-based synthesis use aggregate results reported in the cited publications.^{11,16,17}

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Research Article

BLASTOCYST DEVELOPMENT AND EMBRYO PLOIDY IN WOMEN WITH GENOTYPE-CONFIRMED HPV-ASSOCIATED CIN1: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Human papillomavirus is the most prevalent sexually transmitted viral infection worldwide and is recognized as the principal etiologic factor for cervical intraepithelial neoplasia (CIN) and cervical cancer. While the oncogenic potential of high-risk HPV genotypes has been extensively investigated, their possible influence on female fertility and embryo developmental competence remains controversial. Several clinical studies have evaluated reproductive outcomes in HPV-positive women undergoing assisted reproductive technology (ART), yet the available evidence is inconsistent. Most published reports have focused on implantation, pregnancy, and miscarriage rates, whereas little is known about the effect of HPV-associated CIN1 on blastocyst development and embryonic chromosomal competence. This study aimed to evaluate blastocyst formation and embryo ploidy in women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI treatment with universal PGT-A.

Methods: A retrospective multicenter cohort study was conducted at the Georgian-German Reproduction Center (GGRC) and Caraps Medline, Tbilisi, Georgia, analyzing IVF/ICSI cycles performed between 2024 and 2026. A total of 298 women aged 30-35 years were included: 98 in the HPV-associated CIN1 study group and 200 in the HPV-negative control group. Primary outcomes evaluated were blastulation and euploid embryo rates using PGT-A via next-generation sequencing.

Results: A total of 1,087 embryos were evaluated (388 in the study group and 699 in the control group). The blastulation rate was 43.2% in the HPV-associated CIN1 group versus 54.4% in the control group (\$p < 0.05\$). The euploid embryo rate was 54.3% in the study group versus 61.2% in controls (\$p < 0.05\$).

Conclusion: Women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI demonstrated lower blastulation rates and lower proportions of euploid embryos compared to HPV-negative women, suggesting persistent cervical disease may adversely affect embryo developmental competence before implantation.

Keywords: HPV, CIN1, IVF, ICSI, blastocyst, embryo ploidy, euploidy, PGT-A, HPV vaccination

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Key Messages

- **What is already known on this topic:** High-risk HPV is the primary etiologic factor for cervical dysplasia, but its downstream effects during assisted reproduction have previously focused primarily on clinical pregnancy, implantation, or miscarriage rates rather than upstream pre-transfer embryonic quality.
- **What this study adds:** In a controlled multicenter cohort using universal PGT-A, women with genotype-confirmed HPV-associated CIN1 demonstrated significantly lower blastulation rates (43.2% vs. 54.4%) and reduced euploid embryo rates (54.3% vs. 61.2%) compared to HPV-negative controls.
- **How this study might affect research, practice, or policy:** These findings suggest that persistent cervical HPV infection and associated dysplasia compromise oocyte and embryo developmental competence, indicating that patients with persistent HPV-associated CIN1 may benefit from comprehensive pre-ART reproductive evaluation and counseling.

Introduction

Human papillomavirus infects approximately 80% of sexually active individuals during their lifetime. Persistent infection with high-risk HPV genotypes may result in cervical dysplasia and cervical cancer. Although cervical pathology has been extensively studied from an oncologic perspective, its influence on reproductive biology remains incompletely understood.¹

Successful embryo development depends on multiple maternal and embryonic factors, including oocyte competence, follicular environment, endometrial receptivity, immune regulation, and chromosomal integrity.² Chronic cervical HPV infection may induce persistent local inflammation, oxidative stress, cytokine imbalance, and immune activation, potentially influencing oocyte maturation and embryo development.³

Previous studies investigating HPV and IVF outcomes have produced conflicting results.^{4,5} Some authors reported reduced implantation and increased miscarriage rates, whereas others found no significant effect on ART success. Crucially, few investigations have specifically evaluated embryo quality at the blastocyst stage or embryo chromosomal status using PGT-A. Furthermore, while the prophylactic benefits of HPV vaccination in preventing cervical intraepithelial neoplasia are well established [1.1.4], its broader intersection with reproductive health, oocyte yield, and ART parameters continues to be a subject of clinical evaluation [1.1.1].

The present study was designed to investigate whether women with genotype-confirmed HPV-associated CIN1 demonstrate differences in blastocyst development and embryo euploidy compared with HPV-negative women without cervical dysplasia.

Methods

Study Design

A retrospective multicenter cohort study was performed at the Georgian-German Reproduction Center (GGRC) and Caraps Medline in Tbilisi, Georgia. The study included IVF/ICSI cycles performed between 2024 and 2026. Institutional approval was obtained before data analysis.

Patient Selection

A total of 298 women aged 30-35 years were included.

- **Study Group:** \$n = 98\$ (Genotype-confirmed HPV infection, Histologically confirmed CIN1)
- **Control Group:** \$n = 200\$ (HPV-negative, No cervical dysplasia)

Inclusion Criteria

- Age 30-35 years
- IVF/ICSI treatment
- Available blastocyst culture
- PGT-A performed on all blastocysts
- Complete clinical records
- Histological confirmation of CIN1 (study group)

Exclusion Criteria

- Moderate or severe male factor infertility
- Previous cervical cancer
- CIN2 or CIN3
- Previous chemotherapy
- Previous pelvic radiotherapy
- Uterine malformations
- Recurrent implantation failure
- Recurrent pregnancy loss
- Autoimmune disease

Diagnostic Evaluation

All participants underwent:

- Cervical cytology (Pap test)
- Colposcopy
- HPV genotyping
- Cervical biopsy
- Histopathological confirmation
- Transvaginal ultrasonography
- Standard IVF/ICSI protocol
- Blastocyst culture
- Trophectoderm biopsy
- PGT-A using next-generation sequencing (NGS)⁶⁻⁷

Embryology Procedures

Controlled ovarian stimulation was performed according to individualized ovarian stimulation protocols.

Following oocyte retrieval:

- Mature oocytes underwent ICSI.
- Embryos were cultured until Day 5 or Day 6.
- Blastocysts were graded according to the Gardner classification.⁸
- Suitable blastocysts underwent trophectoderm biopsy.
- Biopsied embryos were vitrified.
- Chromosomal analysis was performed using PGT-A.

Outcome Measures

- **Primary outcomes:** Blastulation rate, Euploid embryo rate.

- **Secondary outcomes:** Number of blastocysts, Number of biopsied embryos, Embryo developmental competence.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation (SD), while categorical variables were expressed as percentages.
Comparisons between groups were performed using Student’s t-test for continuous variables and the χ^2 test or Fisher’s exact test for categorical variables.
A p-value <0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 298 patients met the inclusion criteria. The two groups were comparable regarding maternal age because only women aged 30-35 years were included.
Overall:

- HPV-associated CIN1 group: 98 women
- Control group: 200 women

Embryological Outcomes

Overall, 1,087 embryos underwent evaluation.

- HPV-associated CIN1 group: 388 embryos
- Control group: 699 embryos

Blastulation Rate

The blastulation rate was:

- 43.2% in the HPV-associated CIN1 group
- 54.4% in controls, representing an absolute reduction of 11.2 percentage points (p < 0.05).

Euploid Embryo Rate

The euploid embryo rate was:

- 54.3% in the HPV-associated CIN1 group
- 61.2% in controls

representing an absolute reduction of 6.9 percentage points (p < 0.05).

Summary of Main Findings

Outcome	HPV-Associated CIN1	Controls
Patients	98	200
Embryos analyzed	388	699
Blastulation (blastocyst formation rate)	43.2%	54.4%
Euploid embryos	54.3%	61.2%

Overall, women with genotype-confirmed HPV-associated CIN1 produced fewer blastocysts and a lower proportion of chromosomally normal embryos than HPV-negative women.

Discussion

The present study demonstrated that women with genotype-confirmed HPV-associated CIN1 had lower blastocyst development and lower embryo euploidy rates compared to HPV-negative controls. Several biological mechanisms may explain these observations.

Persistent HPV infection induces chronic inflammation within the cervical microenvironment.⁹ Elevated local and systemic inflammatory cytokines, oxidative stress,¹⁰ and altered immune responses may influence follicular physiology and compromise oocyte competence.¹¹

Furthermore, emerging literature indicates that the biological footprint of human papilloma-virus extends beyond the female lower genital tract. High-risk HPV virions can bind to spermatozoa – specifically targeting head structures and cell membranes – thereby inducing elevated sperm DNA fragmentation (DFI), oxidative membrane deterioration, and activation of the apoptotic pathway [1.1.5]. Because our cohort underwent ICSI, the potential introduction of compromised paternal genomic material, coupled with maternal follicular and microenvironmental stress from cervical dysplasia, may synergistically impair early cleavage divisions and diminish overall blastocyst developmental competence.

Experimental studies have similarly suggested that viral elements can affect mitochondrial function, spindle organization, DNA repair mechanisms, and apoptotic pathways, reducing embryonic developmental potential.¹²

Additionally, the role of preventive measures such as HPV vaccination warrants consideration in reproductive planning. While clinical studies confirm that prior HPV vaccination effectively prevents high-grade cervical dysplasia without impairing baseline ovarian response, oocyte yield, or overall IVF fertilization rates [1.1.1], mitigating primary viral exposure via vaccination remains a cornerstone strategy to protect long-term reproductive tissue integrity.

Although HPV infection primarily manifests in epithelial cells, both local cervical inflammation, potential gamete-level interactions, and immunological prevention dynamics contribute to our understanding of shared reproductive consequences.

The reduction in blastocyst formation observed in the present study supports the hypothesis that HPV-associated CIN1 is associated with impaired embryonic developmental competence. The lower euploid embryo rate may indicate an indirect effect of chronic inflammation on meiotic competence and chromosomal stability, although causality cannot be established in this retrospective analysis.

Our findings are consistent with previous reports exploring reproductive performance in HPV-affected cohorts.^{13,14} However, unlike earlier studies that focused mainly on implantation or miscarriage, the present study evaluated embryonic development before embryo transfer using universal PGT-A across two specialized centers (GGRC and Caraps Medline), adhering strictly to top-tier Medline-indexed obstetric and gynecologic reporting standards.

Clinical Implications

The findings suggest that women diagnosed with persistent HPV-associated CIN1 may benefit from comprehensive reproductive evaluation before IVF.

Potential considerations include:

- HPV genotyping before ART
- Careful colposcopic assessment
- Proactive optimization of cervical health and vaccination status counseling where appropriate
- Individualized clinical counseling

- Consideration of embryo genetic testing when clinically indicated Further research is needed before routine changes in IVF protocols can be recommended.

Strengths

- Multicenter design (GGRC and Caraps Medline)
- Genotype-confirmed HPV infection
- Histologically confirmed CIN1
- Uniform age range
- Universal PGT-A
- Large embryo dataset (1,087 embryos)
- Direct assessment of embryo chromosomal competence

Limitations

The study has several limitations:

- Retrospective design
- Lack of stratification according to specific HPV genotypes
- No evaluation of viral persistence or viral load dynamics
- No assessment of live birth outcomes
- Absence of direct inflammatory biomarker analysis Prospective multicenter studies are required to validate these findings.

Conclusions

Women with genotype-confirmed HPV-associated CIN1 undergoing IVF/ICSI demonstrated lower blastulation rates and lower proportions of euploid embryos compared to HPV-negative women without cervical dysplasia. These findings suggest that persistent HPV-associated cervical disease may adversely affect embryo developmental competence before implantation. Further prospective multicenter investigations incorporating molecular, immunologic, and reproductive biomarkers are warranted to clarify the biological mechanisms underlying these observations and to determine their clinical significance.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no competing interests.

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Research Article

PHYSICIAN-SELECTED TIMING OF FROZEN BLASTOCYST TRANSFER AND CLINICAL PREGNANCY OUTCOMES: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background: Programmed frozen blastocyst transfer requires coordination between progesterone-driven endometrial maturation and embryo development. More than one progesterone exposure window is used in routine practice, and the treating physician may select timing for an individual cycle. This study evaluated whether physician-selected timing was associated with ultrasound-confirmed clinical pregnancy.

Methods: This retrospective single-center cohort included 160 frozen embryo transfer cycles performed at the Georgian-German Reproduction Center during May 2026. Inclusion criteria were endometrial thickness at least 8 mm, serum progesterone below 1 ng/mL before progesterone initiation, and vaginal micronized progesterone 600 mg daily. Cycles using endometrial receptivity testing were excluded. The primary analysis excluded four Day-3 transfers performed before 120 hours, four mixed Day-5 and Day-6 transfers, and two blastocyst transfers performed after 136 hours, leaving 150 Day-5 or Day-6 transfers at 120-126 or 133-136 hours. Clinical pregnancy was defined as ultrasonographic visualization of at least one gestational sac. Fisher exact tests and multivariable logistic regression were used.

Results: Clinical pregnancy occurred in 42 of 80 transfers at 120-126 hours (52.5%) and 34 of 70 transfers at 133-136 hours (48.6%). The later window was not significantly associated with clinical pregnancy in unadjusted analysis (odds ratio 0.85, 95% confidence interval 0.45-1.62; P=0.744) or after adjustment for embryo day, recipient type, oocyte source, oocyte age, and body mass index (adjusted odds ratio 0.84, 95% confidence interval 0.43-1.63; P=0.606). No significant interaction was identified by recipient type, body mass index, or embryo day.

Conclusion: Within the two evaluated exposure windows and standardized programmed-cycle protocol, physician-selected timing was not significantly associated with clinical pregnancy. The findings support continued physician-directed selection of these timing options for appropriately selected cycles, but do not establish equivalence or superiority.

CITATION: Tvauri M, Charkviani T, Nadirashvili T, et al. Physician-selected timing of frozen blastocyst transfer and clinical pregnancy outcomes: A retrospective cohort study. Medical Times. Georgian-German Reproduction Center; 2026;(5):122–133. <https://doi.org/10.71419/mtggrc.2026.38>

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Keywords: assisted reproduction; endometrial preparation; gestational carrier; hormone replacement therapy; luteal support; progesterone exposure; ultrasonography

Introduction

Programmed frozen embryo transfer (FET) uses exogenous estrogen to prepare the endometrium and progesterone to initiate secretory transformation. The duration of progesterone exposure is therefore a central determinant of embryo-endometrium synchronization. Standard protocols commonly schedule blastocyst transfer after approximately five to seven days of progesterone exposure. Still, the optimal interval remains uncertain, and published studies use different definitions of progesterone day and transfer timing.¹⁻³

Evidence comparing adjacent progesterone durations is inconsistent. Some cohort studies have reported comparable outcomes after six or seven days of progesterone exposure,^{3,7} whereas others have identified differences overall or within Day-5, Day-6, or morphological subgroups.^{4-6,8,9} A recent randomized trial of Day-6 blastocysts found comparable overall live birth rates after six or seven days, with an exploratory interaction according to blastocyst expansion stage.¹⁰ These data suggest that the effective implantation window may be sufficiently broad for many cycles but may not be identical across embryo and recipient characteristics.

Most studies compare predefined protocols. In routine care, however, a physician may select among locally accepted timing windows for an individual cycle. This creates a clinically distinct question: whether physician-selected timing, as practiced under a standardized programmed-cycle regimen, is associated with clinical pregnancy. We compared ultrasound-confirmed clinical pregnancy after transfer at 120-126 hours and 133-136 hours of progesterone exposure. We explored whether the association differed by recipient type, body mass index (BMI), embryo developmental day, oocyte source, preimplantation genetic testing status, number of embryos transferred, or blastocyst morphology.

Materials and methods

Study design and setting

This retrospective observational cohort included all eligible embryo-transfer cycles performed at the Georgian-German Reproduction Center (GGRC), Tbilisi, Georgia, during May 2026. The embryo-transfer cycle was the unit of analysis. The treating physician selected Transfer timing during routine clinical care and was not randomized. Accordingly, all effect estimates are interpreted as associations.

Eligibility and programmed-cycle preparation

Eligible cycles used hormone replacement therapy for endometrial preparation. Inclusion criteria were endometrial thickness at least 8 mm, serum progesterone below 1 ng/mL before exogenous progesterone initiation, and vaginal micronized progesterone 600 mg daily, administered as 200 mg three times daily. Cycles using endometrial receptivity testing, including ERA or EndomeTRIO, were excluded. Additional intramuscular progesterone was used in some cycles at physician discretion, but a complete cycle-level record of dose and route was unavailable and therefore could not be analyzed.

Exposure definition and analytical cohort

The exposure was elapsed time from progesterone initiation to embryo transfer, recorded in clinical scheduling categories. The primary comparison was 120-126 hours versus 133-136

hours. The source cohort contained 160 eligible cycles. Four Day-3 cleavage-stage transfers performed before 120 hours were excluded because their developmental stage was not comparable with blastocyst transfer. Four transfers containing both Day-5 and Day-6 blastocysts were excluded to preserve a single embryo-developmental-day classification. Two Day-5 or Day-6 transfers performed after 136 hours were excluded because the group was too small for inference. The primary analytical cohort therefore contained 150 single-stage Day-5 or Day-6 blastocyst transfers.

160 eligible FET cycles performed during May 2026
Excluded from the primary comparison: 4 Day-3 transfers before 120 hours; 4 mixed Day-5 and Day-6 transfers; 2 Day-5 or Day-6 transfers after 136 hours
150 Day-5 or Day-6 blastocyst transfers in the primary analytical cohort
80 transfers at 120-126 hours
70 transfers at 133-136 hours

Figure 1. Cohort flow.

Outcome definition

The primary outcome was clinical pregnancy per embryo-transfer cycle. Clinical pregnancy was defined as ultrasonographic visualization of at least one gestational sac, consistent with international terminology.¹¹ Clinical-pregnancy status was available for all cycles. Cycles with negative serum beta-human chorionic gonadotropin were classified as not achieving clinical pregnancy, whereas ultrasound confirmation was required after a positive biochemical pregnancy test.

Recipient and embryo characteristics

Recipient type referred to the person undergoing embryo transfer. A positive surrogate-mother field indicated a gestational carrier, and a negative field indicated the patient or intended mother. BMI was the BMI of the actual embryo recipient and was grouped as less than 18.5, 18.5-24.9, 25.0-29.9, or at least 30 kg/m2. In regression models, BMI was represented as less than 25, 25.0-29.9, and at least 30 kg/m2.

Oocyte source was classified as own or donor. Oocyte age was the intended mother’s age at retrieval in own-oocyte cycles and the donor’s age at retrieval in donor-oocyte cycles. Other recorded characteristics were embryo developmental day, preimplantation genetic testing result, number of embryos transferred, and blastocyst morphology. Morphological descriptions were parsed using expansion stage, inner cell mass, and trophectoderm grades.^{1,2} Because only three primary-cohort transfers were below a 3BB threshold, morphology was analyzed exploratorily as the presence of at least one AA blastocyst versus non-AA morphology.

Statistical analysis

Categorical data are reported as n/N (%) and continuous data as median (IQR). Fisher’s exact tests were used for 2-by-2 comparisons. Sparse 2-by-k tables were evaluated using Fisher-Freeman-Halton tests with Monte Carlo estimation. Oocyte-age distributions were compared using the two-sided Mann-Whitney U test. Odds ratios (ORs) and 95% confidence intervals (CIs)

were estimated comparing 133-136 hours with 120-126 hours. The absolute risk difference was calculated as the later-window rate minus the earlier-window rate with a Newcombe 95% CI. Two-sided P values below 0.05 were considered statistically significant.

Prespecified subgroup analyses evaluated recipient type, BMI category, embryo developmental day, oocyte source, preimplantation genetic testing status, number of embryos transferred, and AA morphology. Timing interactions with recipient type, BMI, embryo day, oocyte source, and AA morphology were tested in separate logistic models. These subgroup analyses were exploratory and were not adjusted for multiple comparisons.

The primary multivariable logistic regression model included transfer timing, embryo developmental day, recipient type, oocyte source, oocyte age, and recipient BMI. An expanded sensitivity model additionally included normal preimplantation genetic testing status, transfer of two embryos, and AA morphology. Physician was not included in the regression model because timing had minimal overlap across physicians, resulting in near-collinearity between physician and timing. Statistical analyses were conducted using Python, SciPy, and statsmodels.

No a priori sample-size calculation was performed because all eligible cycles during the defined study period were included.

Exploratory second-transfer sequence analysis

A supplemental sequence dataset identified 32 cycles recorded as second transfers and included the progesterone-exposure window used for the preceding transfer. To align this analysis with the primary cohort definition, two Day-3 transfers and one mixed Day-5 and Day-6 transfer were excluded, leaving 29 Day-5 or Day-6 second-transfer cycles within the 120-126-hour or 133-136-hour windows. Cycles were classified as either retaining the progesterone-exposure window from the first transfer or changing it. Clinical pregnancy was compared between the current second-transfer window and retained versus changed timing using Fisher’s exact tests. Sequence-specific rates were considered descriptive because only five cycles involved a change in timing.

Ethics and data governance

This study used retrospective data generated during routine clinical care. Direct patient identifiers were excluded from analytical and publication outputs. GGRC did not have an institutional ethics committee, and no formal ethics approval, exemption, or waiver was issued. No additional intervention or patient contact occurred for research purposes.

Results

Cohort and baseline characteristics

The full cohort contained 160 cycles, of which 83 (51.9%) resulted in clinical pregnancy. After the 10 exclusions shown in Figure 1, the primary analytical cohort comprised 150 transfers and 76 clinical pregnancies (50.7%). The 120-126-hour group included 80 transfers and the 133-136-hour group included 70 transfers.

Recipient type, embryo developmental day, BMI distribution, preimplantation genetic testing status, number of embryos transferred, and AA morphology were similar between timing groups. The later-window group contained a higher proportion of own-oocyte cycles and had a higher median oocyte age (Table 1).

Table 1. Baseline characteristics of the primary analytical cohort.

Characteristic	120-126 hours (n=80)	133-136 hours (n=70)	P value
Embryo day 5	52/80 (65.0%)	48/70 (68.6%)	0.729
Embryo day 6	28/80 (35.0%)	22/70 (31.4%)	
Patient or intended mother	19/80 (23.8%)	21/70 (30.0%)	0.460
Gestational carrier	61/80 (76.2%)	49/70 (70.0%)	
Donor oocytes	63/80 (78.8%)	44/70 (62.9%)	0.046
Own oocytes	17/80 (21.2%)	26/70 (37.1%)	
Oocyte age, median (IQR)	25.0 (22.8-29.0)	27.0 (23.0-32.8)	0.039
BMI less than 18.5 kg/m2	4/80 (5.0%)	3/70 (4.3%)	0.966
BMI 18.5-24.9 kg/m2	33/80 (41.2%)	31/70 (44.3%)	
BMI 25.0-29.9 kg/m2	27/80 (33.8%)	24/70 (34.3%)	
BMI at least 30 kg/m2	16/80 (20.0%)	12/70 (17.1%)	
Normal PGT result	71/80 (88.8%)	59/70 (84.3%)	0.476
Two embryos transferred	7/80 (8.8%)	4/70 (5.7%)	0.544
At least one AA blastocyst	46/80 (57.5%)	46/70 (65.7%)	0.319

BMI, body mass index; IQR, interquartile range; PGT, preimplantation genetic testing. P-values compare distributions across timing groups.

Primary timing comparison

Clinical pregnancy occurred in 42 of 80 transfers at 120-126 hours (52.5%) and 34 of 70 transfers at 133-136 hours (48.6%). The absolute difference between the later and earlier window was -3.9 percentage points (95% CI, -19.4 to 11.8). The unadjusted timing association was not statistically significant (OR 0.85, 95% CI 0.45-1.62; P=0.744).

Table 2. Clinical pregnancy by progesterone exposure window.

Timing window	Transfers	Clinical pregnancies	Clinical pregnancy rate	OR (95% CI)	P value
120-126 hours	80	42	52.5%	Reference	
133-136 hours	70	34	48.6%	0.85 (0.45-1.62)	0.744

CI, confidence interval; OR, odds ratio. The OR compares 133-136 hours with 120-126 hours.

Recipient type and timing

Among patients or intended mothers, clinical pregnancy occurred in 12/19 (63.2%) transfers at 120-126 hours and 9/21 (42.9%) at 133-136 hours (OR 0.44, 95% CI 0.12-1.56; P=0.225). Among gestational carriers, corresponding rates were 30/61 (49.2%) and 25/49 (51.0%) (OR 1.08, 95% CI 0.51-2.28; P=1.000). The timing-by-recipient interaction was not statistically significant (P=0.132).

Recipient type was not significantly associated with clinical pregnancy within either timing window (P=0.308 at 120-126 hours and P=0.607 at 133-136 hours).

Table 3. Clinical pregnancy by recipient type and progesterone exposure window.

Recipient type	120-126 hours	133-136 hours	Late vs early OR (95% CI)	P value
Patient or intended mother	12/19 (63.2%)	9/21 (42.9%)	0.44 (0.12-1.56)	0.225
Gestational carrier	30/61 (49.2%)	25/49 (51.0%)	1.08 (0.51-2.28)	1.000

Values are clinical pregnancies/transfers (%). Timing-by-recipient interaction P=0.132.

Recipient BMI and timing

Clinical pregnancy rates varied across BMI cells, but BMI was not significantly associated with outcome within the 120-126-hour window (P=0.519) or the 133-136-hour window (P=0.439). The timing-by-BMI interaction was not statistically significant (P=0.180). The underweight subgroup and several patient-specific BMI cells were sparse, limiting precision.

Table 4. Clinical pregnancy by recipient BMI and progesterone exposure window.

Recipient type	120-126 hours	133-136 hours	Late vs early OR (95% CI)	P value
Less than 18.5	2/4 (50.0%)	1/3 (33.3%)	0.50 (0.02-11.09)	1.000
18.5-24.9	16/33 (48.5%)	13/31 (41.9%)	0.77 (0.29-2.06)	0.625
25.0-29.9	13/27 (48.1%)	15/24 (62.5%)	1.79 (0.59-5.50)	0.400
At least 30	11/16 (68.8%)	5/12 (41.7%)	0.32 (0.07-1.55)	0.250

Values are clinical pregnancies/transfers (%). Timing-by-BMI interaction P=0.180.

Embryo developmental day

For Day-5 blastocysts, clinical pregnancy occurred in 29/52 (55.8%) transfers at 120-126 hours and 24/48 (50.0%) at 133-136 hours. For Day-6 blastocysts, corresponding rates were 13/28 (46.4%) and 10/22 (45.5%). Neither subgroup comparison nor the timing-by-embryo-day interaction was significant (interaction P=0.729).

Table 5. Clinical pregnancy by embryo developmental day and progesterone exposure window.

Embryo day	120-126 hours	133-136 hours	Late vs early OR (95% CI)	P value
Day 5	29/52 (55.8%)	24/48 (50.0%)	0.79 (0.36-1.74)	0.689
Day 6	13/28 (46.4%)	10/22 (45.5%)	0.96 (0.31-2.95)	1.000

Values are clinical pregnancies/transfers (%). Timing-by-embryo-day interaction P=0.729.

Oocyte source, genetic testing, embryo number, and morphology

No statistically significant timing difference was identified within donor-oocyte, own-oocyte, normal-PGT, non-normal or untested, single-embryo, double-embryo, AA-morphology, or non-AA-morphology subgroups (Table 6). Timing of interactions with the oocyte source and AA morphology was also not significant. The non-normal or untested, two-embryo, and below-3BB groups were small and are interpreted descriptively.

Table 6. Clinical pregnancy by selected cycle characteristics.

Characteristic	120-126 hours	133-136 hours	Late vs early OR (95% CI)	P value
Donor oocytes	31/63 (49.2%)	23/44 (52.3%)	1.13 (0.52-2.44)	0.845
Own oocytes	11/17 (64.7%)	11/26 (42.3%)	0.40 (0.11-1.41)	0.215
Normal PGT	40/71 (56.3%)	29/59 (49.2%)	0.75 (0.37-1.50)	0.481
No normal PGT result	2/9 (22.2%)	5/11 (45.5%)	2.92 (0.41-20.90)	0.374
One embryo	40/73 (54.8%)	33/66 (50.0%)	0.82 (0.42-1.61)	0.612
Two embryos	2/7 (28.6%)	1/4 (25.0%)	0.83 (0.05-13.63)	1.000
At least one AA blastocyst	21/46 (45.7%)	22/46 (47.8%)	1.09 (0.48-2.48)	1.000
Non-AA morphology	21/34 (61.8%)	12/24 (50.0%)	0.62 (0.21-1.78)	0.427

Values are clinical pregnancies/transfers (%). Timing-by-oocyte-source interaction P=0.177; timing-by-AA-morphology interaction P=0.967. PGT, preimplantation genetic testing.

Multivariable analyses

After adjustment for embryo developmental day, recipient type, oocyte source, oocyte age, and BMI, transfer at 133-136 hours was not significantly associated with clinical pregnancy (adjusted OR 0.84, 95% CI 0.43-1.63; P=0.606). None of the prespecified covariates were statistically significant in the primary model (Table 7).

The expanded model additionally adjusted for normal PGT status, transfer of two embryos, and AA morphology. The timing estimate remained materially unchanged (adjusted OR 0.85, 95% CI 0.43-1.68; P=0.648).

Table 7. Primary multivariable logistic regression model for clinical pregnancy.

Variable	Adjusted OR	95% CI	P value
133-136 vs 120-126 hours	0.84	0.43-1.63	0.606
Day 6 vs Day 5	0.77	0.39-1.54	0.463
Gestational carrier vs patient	0.88	0.39-1.97	0.755
Own vs donor oocytes	0.94	0.30-2.96	0.919
Oocyte age, per year	1.01	0.93-1.09	0.843
BMI 25.0-29.9 vs less than 25	1.48	0.71-3.09	0.291
BMI at least 30 vs less than 25	1.56	0.64-3.81	0.326

BMI, body mass index; CI, confidence interval; OR, odds ratio. Reference categories were 120-126 hours, Day 5, patient or intended mother, donor oocytes, and BMI <25 kg/m2.

Physician selection of transfer timing

Transfer timing was strongly associated with physician practice. One anonymized physician performed 63 of 70 later-window transfers (90.0%) but only 4 of 80 earlier-window transfers (5.0%). The remaining physicians performed 7 later-window and 76 earlier-window transfers (Fisher exact P<0.001). Because timing and physician were nearly separated, a physician-adjusted model would be unstable and would not reliably distinguish timing effects from physician-specific case selection or practice patterns. Physician-specific pregnancy rates were therefore not reported.

Exploratory second-transfer sequence analysis

Among 29 eligible second-transfer cycles, the progesterone-exposure window used for the first transfer was retained in 24 cycles (82.8%) and changed in 5 cycles (17.2%). Clinical pregnancy occurred in 8 of 24 cycles (33.3%) when timing was unchanged and in 2 of 5 cycles (40.0%) when timing was changed (OR 1.33, 95% CI 0.18-9.66; Fisher exact P=1.000). When second transfers were classified according to their current progesterone-exposure window, clinical pregnancy occurred in 5 of 14 cycles (35.7%) at 120-126 hours and in 5 of 15 cycles (33.3%) at 133-136 hours (OR 0.90, 95% CI 0.19-4.17; Fisher exact P=1.000).

Table 8. Clinical pregnancy according to first- and second-transfer progesterone exposure windows.

First-transfer timing	Second-transfer timing	Cycles, n	Clinical pregnancy, n/N (%)
120-126 hours	120-126 hours	12	3/12 (25.0%)
120-126 hours	133-136 hours	3	0/3 (0%)
133-136 hours	120-126 hours	2	2/2 (100.0%)
133-136 hours	133-136 hours	12	5/12 (41.7%)

Values are ultrasound-confirmed clinical pregnancies per second-transfer cycle. The changed-timing sequences contained only three and two cycles and are presented descriptively; they should not be interpreted as evidence that changing timing improves outcome.

Discussion

Principal findings

In this real-world cohort of programmed frozen blastocyst transfers, clinical pregnancy occurred in 52.5% of transfers at 120-126 hours and 48.6% at 133-136 hours. The absolute difference was -3.9 percentage points, and neither the unadjusted nor adjusted comparison was statistically significant. The confidence interval remained wide and compatible with a clinically meaningful difference in either direction, so the findings do not establish equivalence.

The association between timing and clinical pregnancy did not differ significantly by recipient type, BMI, or embryo developmental day. Patient cycles showed a numerical reduction in clinical pregnancy in the later window. In contrast, gestational-carrier outcomes were similar across timing groups, but the timing-by-recipient interaction was not significant. BMI-specific rates varied across small cells without a consistent gradient, and no timing-by-BMI interaction was detected. Day-5 and Day-6 blastocysts also showed similar timing patterns.

Timing estimates remained stable after multivariable adjustment and after adding PGT status, number of embryos transferred, and AA morphology. The principal methodological feature was the strong relationship between the physician and the timing of selection. This reflects the clinical question under study and physician-selected timing, but also prevents separating a biological timing effect from physician-specific selection and workflow.

Relation to existing evidence

The published literature is heterogeneous because progesterone day is defined differently across studies and comparisons range from several hours to a full day. Roelens et al. reported similar live birth rates after six or seven days of progesterone exposure in programmed cycles.³ In contrast, a propensity score-matched cohort by Yang et al. favored six days overall, particu-

larly in younger patients and selected embryo subgroups.⁴ Liu et al. found no significant difference in clinical outcomes across progesterone durations in artificial cycles.⁵

More recent studies have continued to produce mixed results. Zhou et al. reported comparable overall live birth rates after six or seven days, but a higher live birth rate with seven days among Day-6 blastocysts.⁶ Large Day-6 blastocyst cohorts have reported either comparable outcomes after six or seven days⁷ or higher pregnancy and live birth rates with six rather than five days.⁹ In an oocyte-donation cohort, extending vaginal progesterone from five to six days did not improve outcomes.⁸ A 2026 randomized trial found comparable overall live birth rates for Day-6 blastocysts after six or seven days, although exploratory analyses suggested that expansion stage may modify the effect.¹⁰

The present study differs from these protocol comparisons by evaluating two narrower timing categories selected by physicians in routine practice and including both Day-5 and Day-6 blastocysts. Its findings, therefore, inform the use of physician judgment within the specific standardized regimen studied rather than defining a universally optimal duration of progesterone.

Clinical interpretation

Within this clinic protocol, physician selection between 120-126 and 133-136 hours was not associated with a statistically detectable difference in clinical pregnancy. This supports continued physician-directed use of either window for appropriately selected cycles when endometrial preparation, baseline progesterone, and vaginal progesterone administration are standardized. The result should not be interpreted as evidence that timing is arbitrary or that all progesterone durations are interchangeable.

The exploratory second-transfer analysis should be interpreted as descriptive rather than as a basis for changing clinical practice. Physicians retained the previously used timing window in most second-transfer cycles, and no clear clinical-pregnancy difference was observed when timing was retained versus when it was changed. Because only five cycles involved a change in timing, the data do not support recommending either routine retention or routine modification of the previous window.

The patient and gestational-carrier subgroup findings should not be used to prescribe different windows because interaction testing was negative and subgroup confidence intervals were wide. Similarly, the BMI and embryo-day analyses did not identify a reproducible modifier. The study does not address substantially earlier or later transfers, different progesterone routes or doses, natural-cycle FET, ongoing pregnancy, or live birth.

Strengths and limitations

Strengths include inclusion of all eligible cycles during a defined period, explicit accounting for the transition from 160 source cycles to 150 primary-analysis transfers, complete clinical-pregnancy ascertainment, standardized endometrial thickness and baseline progesterone criteria, a uniform vaginal progesterone dose, detailed analyses by recipient type, BMI, embryo day, oocyte source, genetic testing, embryo number, and morphology, and a linked exploratory analysis of first-to-second transfer timing sequences. Clinical pregnancy was defined using internationally standardized terminology.¹¹

The study is limited by its retrospective, non-randomized design, single-center setting, one-month study period, and modest sample size. Timing was highly concentrated among a single physician, creating residual confounding and preventing reliable physician adjustment. Sub-

group cells were sparse, particularly for patients at BMI extremes, transfers of two embryos, non-normal PGT categories, and blastocysts below 3BB. The second-transfer sequence analysis included only 29 eligible cycles, and only five involved a change in timing, resulting in highly imprecise sequence-specific estimates. Oocyte age differed between timing groups and represented donor age in donor cycles and intended-mother age in own-oocyte cycles. Additional intramuscular progesterone use was incompletely recorded. Clinical pregnancy is more clinically meaningful than beta-hCG positivity, but ongoing pregnancy and live birth were unavailable. Finally, no formal ethics approval, exemption, or waiver was issued, which may affect journal eligibility.

Conclusion

Among single-stage Day-5 and Day-6 blastocyst transfers performed after 120-126 or 133-136 hours of progesterone exposure, physician-selected timing was not significantly associated with ultrasound-confirmed clinical pregnancy. No statistically significant modification was identified by recipient type, BMI, embryo developmental day, oocyte source, or AA morphology. The findings support physician-directed selection between the two studied windows within the standardized programmed FET protocol. In contrast, strong physician-linked timing selection and wide confidence intervals preclude conclusions regarding equivalence, superiority, or a universally optimal transfer time.

Declarations

Author contributions

Mariam Tvauri: Conceptualization, methodology, investigation, data curation, formal analysis, project administration, visualization, interpretation, and writing of the original draft. Tea Charkviani: Methodology, validation, clinical interpretation, supervision, and writing-review and editing. Tamara Nadirashvili, Oliko Murgulia, Ivane Kutivadze, Tamar Magularia, Mery Natroshvili, and Ana Aivazova: Investigation, clinical data acquisition, source-data validation, clinical interpretation, and writing-review and editing. Nino Museridze: Resources, clinical oversight, supervision, interpretation, and writing-review and editing. All authors reviewed and approved the final manuscript and agree to be accountable for the integrity of the work.

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Data availability: The source data, including the supplemental second-transfer sequence dataset, are not publicly available because they derive from clinical records. A de-identified analytical dataset may be considered upon reasonable request to the corresponding author, subject to institutional authorization and applicable privacy requirements.

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Supplementary analyses

Supplementary Table S1 presents BMI-specific clinical pregnancy rates separately for patients or intended mothers and gestational carriers. These cells are descriptive because several denominators are small.

Supplementary Table S1. Clinical pregnancy by recipient type, BMI, and progesterone exposure window.

Recipient type	Timing, hours	BMI, kg/m2	Clinical pregnancy
Patient	120-126	Less than 18.5	1/2 (50.0%)
Patient	120-126	18.5-24.9	6/10 (60.0%)
Patient	120-126	25.0-29.9	3/5 (60.0%)
Patient	120-126	At least 30	2/2 (100.0%)
Patient	133-136	Less than 18.5	0/0 (-)
Patient	133-136	18.5-24.9	1/7 (14.3%)
Patient	133-136	25.0-29.9	5/9 (55.6%)
Patient	133-136	At least 30	3/5 (60.0%)
Gestational carrier	120-126	Less than 18.5	1/2 (50.0%)
Gestational carrier	120-126	18.5-24.9	10/23 (43.5%)
Gestational carrier	120-126	25.0-29.9	10/22 (45.5%)
Gestational carrier	120-126	At least 30	9/14 (64.3%)
Gestational carrier	133-136	Less than 18.5	1/3 (33.3%)
Gestational carrier	133-136	18.5-24.9	12/24 (50.0%)
Gestational carrier	133-136	25.0-29.9	10/15 (66.7%)
Gestational carrier	133-136	At least 30	2/7 (28.6%)

Values are clinical pregnancies/transfers (%). Exact omnibus BMI-outcome P values were 0.905 and 0.277 in patient cycles at 120-126 and 133-136 hours, respectively, and 0.684 and 0.389 in gestational-carrier cycles.

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Research Article

BEYOND EMBRYO QUALITY:
ENDOMETRIAL FACTORS
IN 66 CRYOPRESERVED EMBRYO TRANSFERS

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ABSTRACT

Background: Cryopreserved embryo transfer now accounts for the majority of transfers in many programs, and embryo selection using preimplantation genetic testing for aneuploidy (PGT-A) has reduced, but not eliminated, implantation failure. 1,4 When implantation fails despite the transfer of euploid embryos, attention turns to the endometrium – its receptivity timing, assessed by Endometrial Receptivity Analysis (ERA), 2,3,5 and its microbial composition, assessed by endometrial microbiome metagenomic analysis (EMMA).6,8 Both tests are offered routinely in this program, but their yield and their relationship to each other have not previously been audited.

Methods: Retrospective single-center cohort study of 66 cryo ET cycles performed in 35 patients between February 2024 and August 2026, using the clinic cycle register together with data from 40 ERA and 36 EMMA reports (Igenomix, processed at Avrupa Laboratories). Donor status was assigned per transfer by matching each transfer to its originating oocyte pick-up cycle by cryopreservation date rather than by patient-level flag. Pregnancy outcome was classified as clinical, biochemical, negative, or pending. ERA recommendations were recorded as hours of progesterone administration and compared with the biopsy protocol. EMMA reports were parsed for all panel organisms. The association between ERA timing and EMMA status was tested using point-biserial correlation, Mann-Whitney U, and Fisher exact tests, with sensitivity analyses for outliers and a Bonferroni correction.

Results: Of 58 transfers with a recorded outcome, 23 resulted in a positive pregnancy test (39.7%), comprising 14 clinical (24.1%) and 9 biochemical pregnancies; thus, biochemical losses accounted for 39.1% of all positive tests. Donor oocytes were used in 37 of 66 transfers (56.1%), and 53 transfers (80.3%) used PGT-A euploid embryos. Among 40 ERAs, the modal recommended duration was 127 hours of progesterone (9/31, 29.0%); however, in all 25 receptive reports that carried a numeric hour, the recommendation reproduced the biopsy protocol

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exactly, so the modal value reflects clinic practice rather than a biological optimum. Of the 35 women with an interpretable result, 8 (22.9%) had a displaced window of implantation. Five of 40 reports (12.5%) were technical failures. Among 36 EMMA reports, *Gardnerella vaginalis* was the most common pathogenic organism (10/36, 27.8%); *Bifidobacterium* spp was detected more often (33.3%) but is not classed as pathogenic. In the 29 women with both tests, no association was found between ERA timing and EMMA findings (all $p \geq 0.38$ after sensitivity analysis and correction for multiple testing).

Conclusion: In a programme dominated by euploid embryos and donor oocytes, the clinical pregnancy rate per transfer was 24.1%, and 39.1% of positive tests were biochemical – a proportion high enough to warrant investigation and consistent with reports that biochemical loss is not explained by embryo chromosomal status.^{9,10} Endometrial receptivity testing identified a displaced window in roughly one woman in five, which is its clinically useful yield, but the modal hour must not be read as an optimal transfer time. ERA and EMMA showed no relationship to one another and should be interpreted as independent sources of information. Sample size, pending outcomes, and the absence of linkage between test results and transfer outcomes limit the analysis.

Patients are identified throughout by sequential codes (P01-P35) and oocyte donors by pseudonymous codes (D01-D21). No names, record numbers or original donor identifiers appear in this document.

Keywords: biochemical pregnancy; embryo implantation; endometrial microbiome; endometrial receptivity; euploid embryo transfer; preimplantation genetic testing for aneuploidy (PGT-A)

Transfer volume

Sixty-six cryo ET cycles were performed across 35 individual patients, a mean of 1.9 transfers per patient. Roughly two-thirds of patients underwent more than one transfer within the review window:

Table 1. Distribution of transfers per patient. No patient in the cohort underwent more than three transfers.

Transfers per patient	Patients	Transfers contributed	% of all transfers
1 transfer	11	11	16.7%
2 transfers	17	34	51.5%
3 transfers	7	21	31.8%
Total	35	66	100%

The repeat-transfer pattern matters when interpreting the headline rate: because 24 of 35 patients contributed two or three cycles each, the per-transfer rate reported below is not equivalent to a per-patient cumulative success rate, which would be higher.

Pregnancy outcomes

Outcomes were recorded for 58 of the 66 transfers. The remaining 8 have no result entered – these are almost entirely transfers dated late July and early August 2026, for which results were still pending at the time of extraction. All rates below therefore use 58 as the denominator.

Table 2. Outcome distribution across all 66 transfers.

Outcome	n	% of 58 with a result	% of all 66
Clinical pregnancy	14	24.1%	21.2%
Biochemical pregnancy	9	15.5%	13.6%
Negative	35	60.3%	53.0%
Result pending	8	-	12.1%
Total	66	100%	100%

Headline rates

- Positive pregnancy test per transfer (clinical + biochemical): 23 / 58 = 39.7%
- Clinical pregnancy per transfer: 14 / 58 = 24.1%
- Negative per transfer: 35 / 58 = 60.3%

The gap between the two headline figures is substantial and deserves emphasis. Of the 23 positive tests, 9 (39.1%) were biochemical – that is, a positive hCG that did not progress to a clinical pregnancy. Quoting the 39.7% figure without that qualifier materially overstates the outcome that patients care about. Early pregnancy loss at this rate is a finding worth monitoring in its own right, particularly given that the great majority of these transfers used euploid, PGT-A-screened embryos. Published series likewise report that biochemical loss is largely independent of embryonic developmental stage and chromosomal constitution,¹⁰ and a large cohort combining PGT-A, ERA, and donor oocytes found biochemical loss attributable to neither the embryo nor the endometrium.⁹

Donor oocyte use

Donor oocytes were used in 37 of the 66 transfers (56.1%); 25 transfers (37.9%) used the patient’s own oocytes; and 4 transfers (6.1%) could not be confidently assigned. At the patient level, 19 of 35 patients (54.3%) had at least one donor-oocyte cycle. Twenty-one distinct donors are represented; one donor (D01) contributed to cycles in two different patients.

Table 3. Oocyte source at transfer level.

Oocyte source	Transfers	% of 66
Donor oocyte	37	56.1%
Patient’s own oocyte	25	37.9%
Undetermined	4	6.1%

Assigning donor status is the least straightforward part of this dataset. Several patients underwent multiple oocyte pick-up (OPU) cycles, of which only one carries a donor code in the source register. Each transfer was therefore matched to its originating OPU cycle by cryopreservation date rather than by taking the patient-level donor flag at face value. This affects five patients: P01, P17, P25, P27 and P28. Taking the patient-level flag uncritically would have classified 40 transfers as donor and 26 as own – a three-transfer overstatement of donor use.

PGT-A status

The cohort is overwhelmingly PGT-A. Fifty-three transfers (80.3%) used embryos with a PGT-A result recorded as euploid. A further 6 transfers were mixed – a euploid-tested embryo was transferred alongside an untested embryo. Only 4 transfers were explicitly untested, and 3 transfers carry no PGT-A entry at all.

Table 4. PGT-A status at transfer level. The 6 mixed transfers are also counted within the 53 in the source register’s own summary; they are separated here to avoid double-counting.

PGT-A status	Transfers	% of 66
Tested, euploid	53	80.3%
Mixed (1 tested + 1 untested)	6	9.1%
Not tested	4	6.1%
No entry recorded	3	4.5%

Because only 4 transfers were unambiguously untested, this dataset cannot support any comparison of tested versus untested outcomes. Four cycles is far too small a group to yield a meaningful rate, and any apparent difference would be noise. The practical reading is that the 39.7% positive-test and 24.1% clinical rate reported above are, in effect, the rates for a euploid-embryo transfer program. Randomized data indicate that PGT-A improves outcomes primarily in older patients, not universally.⁴

Endometrial receptivity (ERA)

Endometrial Receptivity Analysis (ERA) is a transcriptomic assay that dates the endometrium using expression profiles of a panel of receptivity genes and reports the timing of progesterone exposure at which the implantation window opens.¹ Reports were available for 40 women – the 35 patients in the transfer cohort plus 5 women (X36-X40) who were tested but have no transfer recorded in the cycle register. ERA determines whether the endometrium is receptive after a defined duration of progesterone exposure, and expresses its recommendation as the number of hours of progesterone administration at which blastocyst transfer should be performed.

Distribution of test verdicts

Table 5. ERA verdicts across all 40 reports. Five reports (12.5%) failed technically – non-informative, invalid or insufficient RNA – against a manufacturer-quoted combined failure rate of roughly 2.7%.

ERA verdict	n	% of 40	Interpretation
Receptive	27	67.5%	Window of implantation in the expected place
Late receptive	5	12.5%	Transfer 12 h earlier than the biopsy protocol
Pre-receptive	3	7.5%	Window displaced later; 2 of 3 needed a repeat biopsy
Non-informative	2	5.0%	Profile matched no control; repeat biopsy advised
Invalid RNA	2	5.0%	Poor-quality genetic material; repeat biopsy
Insufficient RNA	1	2.5%	Too little genetic material; repeat biopsy

Recommended hour of transfer

A numeric hour could be extracted from 31 of the 40 reports. The remaining 9 comprised the 5 technical failures, 2 pre-receptive results issued without a recommendation pending a second biopsy, and 2 receptive results expressed only as cycle days (P+5 and P+6), with no hour stated.

Table 6. Distribution of ERA-recommended hours of progesterone administration (n = 31). The modal value is highlighted.

Recommended hour	Patients	Share of 31
113 h	1	3.2%
114 h	1	3.2%
115 h	2	6.5%
120 h	4	12.9%
121 h	1	3.2%
122 h	1	3.2%
125 h	2	6.5%
126 h	8	25.8%
127 h	9	29.0%
128 h	1	3.2%
152 h	1	3.2%

Verdict – the most frequently recommended hour is 127 hours of progesterone administration, in 9 of 31 patients (29.0%). Together, 126 h and 127 h account for 17 of 31 (54.8%). Median 126 h; range 113-152 h.

What the modal hour does and does not mean

This figure needs an important qualification, and it is the single most consequential point in this section. For a receptive result, ERA does not compute a new time – it endorses the protocol that was already used. We verified this directly: in all 25 receptive reports carrying a numeric hour, the recommended hour was identical to the hours of progesterone administration recorded for the biopsy cycle itself, with no exceptions.

The modal value of 127 hours therefore reflects the clinic’s standard biopsy protocol, not a biological property observed in these patients. Reading it as “the optimal hour for embryo transfer in this population” would invert cause and effect. The tight 120-128 h cluster reflects consistency of clinic practice; the spread within it corresponds to when each patient actually started progesterone relative to the biopsy.

Randomized evidence on whether acting on displaced results improves live birth is conflicting: a multicentre trial reported higher cumulative rates with receptivity-guided transfer,² whereas a double-blind randomized trial found no difference in live birth and a subsequent analysis argued the test may reduce success by misidentifying the window.^{3,5} The informative results here are the 8 displaced cases. Five late-receptive patients (P03, P04, P08, P28, P31) were moved 12 hours earlier, to 113-125 h. Three pre-receptive patients were moved later or required a repeat biopsy, including P27 at 152 hours – a full day beyond the standard protocol and the widest displacement in the series. In these data, 8 of 35 women with an interpretable

result (22.9%) had a window of implantation that did not align with the standard protocol assumption, which is the clinically useful yield of the test.

Endometrial microbiome (EMMA / ALICE)

Endometrial Microbiome Metagenomic Analysis (EMMA) quantifies bacterial DNA in endometrial tissue; a Lactobacillus-dominated profile has been associated with higher implantation and pregnancy rates, whereas non-Lactobacillus-dominated profiles have been associated with poorer outcomes.^{6,8} Reports were available for 36 women. Each covers three panels: Lactobacillus species; a chronic endometritis pathogen panel (the ALICE panel);⁷ and a broader reproductive tract bacteria panel. Lactobacillus spp was detected in 30 of 36 women (83.3%).

Organisms detected

Table 7. All organisms detected across 36 EMMA reports. Chlamydia trachomatis, Neisseria gonorrhoeae, Mycobacterium tuberculosis, Treponema pallidum, Staphylococcus aureus, Enterococcus faecalis, Mycoplasma genitalium and the remaining panel members were not detected in any patient.

Organism	Patients	% of 36	Panel
Bifidobacterium spp	12	33.3%	Reproductive tract
Gardnerella vaginalis	10	27.8%	Reproductive tract
Ureaplasma urealyticum	5	13.9%	ALICE – chronic endometritis
Atopobium vaginae	3	8.3%	Reproductive tract
Sneathia spp	2	5.6%	Reproductive tract
Streptococcus agalactiae (GBS)	2	5.6%	ALICE – chronic endometritis
Mycoplasma hominis	1	2.8%	ALICE – chronic endometritis
Escherichia coli	1	2.8%	ALICE – chronic endometritis
Klebsiella pneumoniae	1	2.8%	ALICE – chronic endometritis
Mobiluncus spp	1	2.8%	Reproductive tract
Fusobacterium nucleatum	1	2.8%	Reproductive tract
Prevotella bivia	1	2.8%	Reproductive tract
Prevotella disiens	1	2.8%	Reproductive tract

Seventeen of 36 women (47.2%) had at least one organism detected. Excluding Bifidobacterium, 15 of 36 (41.7%) did. Seven of 36 (19.4%) carried at least one organism from the ALICE chronic-endometritis panel.

Which organism counts as “the most common infection”

- The answer depends on what is meant by infection, and the distinction matters clinically.
- Bifidobacterium spp is the most frequently detected organism overall (12/36, 33.3%) – but it is not a pathogen. The reports explicitly state that Bifidobacterium, when detected alone, can often be displaced from its niche by probiotics. Counting it as an infection would overstate the burden by roughly a third.

- Gardnerella vaginalis is the most common clinically relevant pathogenic organism (10/36, 27.8%). It is the organism most commonly associated with bacterial vaginosis and endometrial dysbiosis^{6,8}, and its detection prompted the metronidazole-plus-probiotic recommendation in these reports.
- Ureaplasma urealyticum is the most common organism on the ALICE chronic-endometritis panel specifically (5/36, 13.9%).

Verdict – Gardnerella vaginalis is the most common infectious organism, found in 10 of 36 patients (27.8%). Bifidobacterium spp is detected more often (33.3%) but is not classed as pathogenic. Within the chronic endometritis panel alone, Ureaplasma urealyticum leads with 13.9%.

Detected organisms clustered rather than appearing in isolation. P34 carried six organisms simultaneously (Atopobium, Bifidobacterium, Fusobacterium nucleatum, Gardnerella, Prevotella bivia and Prevotella disiens) at values up to 7.79 against a reference ceiling of 4.22 – a marked polymicrobial dysbiosis. P26 carried five. Nine of the ten Gardnerella-positive women had at least one additional organism, consistent with the mixed anaerobic pattern typical of bacterial vaginosis rather than single-organism infection.^{6,8} Chronic endometritis is common in women with repeated implantation failure, and reproductive outcomes improve after antibiotic treatment, which is the rationale for screening.^{7,11}

Relationship between ERA timing and EMMA findings

Twenty-nine women had both an interpretable ERA hour and an EMMA report, allowing the two to be compared directly. Four pre-specified comparisons were conducted to test whether the recommended transfer hour differed by microbiological status.

Table 7. Point-biserial correlation between EMMA status and ERA-recommended hour (n = 29). Rank-based Mann-Whitney tests yielded p-values of 0.45, 0.67, 0.90, and 0.115, respectively.

Comparison	Detected (n, mean h)	Not detected (n, mean h)	r	p
Any organism	15 – 125.7 h	14 – 123.4 h	+0.17	0.383
Excluding Bifidobacterium	13 – 125.6 h	16 – 123.8 h	+0.13	0.498
Gardnerella vaginalis	9 – 123.1 h	20 – 125.3 h	−0.15	0.444
ALICE-panel organism	6 – 129.8 h	23 – 123.3 h	+0.39	0.037

The one nominally significant result is an artefact

Three of the four comparisons are unambiguously null. The fourth – ALICE-panel organisms – returned **p = 0.037**, which would conventionally be called significant. It should not be reported as a finding, for three independent reasons:

- A single patient drives it. P27 combined the series’ most extreme ERA result (152 h, pre-receptive) with a Streptococcus agalactiae detection. Removing her alone collapses the association from $r = +0.39$, $p = 0.037$ to $r = +0.18$, $p = 0.360$.
- It does not survive correction for multiple testing. Four comparisons were made; the Bonferroni-corrected p is $0.037 \times 4 = 0.148$.
- The rank-based test never agreed. Mann-Whitney yielded $p = 0.115$ for the same data, indicating that the parametric result depends on the outlier’s magnitude rather than on a consistent shift between groups.

Two further checks were also null: the number of organisms detected did not correlate with the recommended hour (Spearman $\rho = +0.14$, $p = 0.459$), and a displaced window of implantation was no more likely in women with an organism detected than in those without (odds ratio 1.05, Fisher exact $p = 1.00$).

Verdict – no association was found between endometrial receptivity timing and endometrial microbiome findings. Every comparison that survives basic robustness checks is null.

How to read a null result here

This is a negative finding, not evidence of absence. With 29 paired cases and only 6 to 15 women in each exposed group, the analysis could only have detected a very large effect – a shift of roughly 5 to 6 hours or more between groups. A real but modest relationship, of the size that would plausibly matter in practice, would be invisible at this sample size. The honest conclusion is that these data neither support nor exclude a link.

It is also worth noting that no strong mechanistic reason to expect one has been established. ERA measures the transcriptomic timing of endometrial receptivity; EMMA measures bacterial DNA present in the same tissue. Both have been separately associated with implantation failure^{1,6}, but that does not imply they are associated with each other; a large cohort applying PGT-A, ERA, and endometrial assessment together likewise failed to attribute early loss to either compartment.⁹ The practical implication is that these two tests appear to capture independent information, and a normal result on one gives no reassurance about the other – which is an argument for interpreting them separately rather than as a combined score.

Limitations

- Pending results. Eight transfers have no recorded outcome. If those cycles ultimately differ from the cohort average, the reported rates will shift; they should be recomputed once results are entered.
- Unconfirmed donor status. P17's 10.07.2025 transfer came from embryos frozen on 10.03.2025, and no matching OPU row exists in the source register for that cycle. Her only listed OPU (27.01.2026) is a donor cycle, so the donor status for this transfer is inferred rather than confirmed.
- No stratified rates. Donor status is reliably known at patient level but only partially reconstructed at transfer level, and the untested group is too small for comparison. Outcomes are therefore not broken down by oocyte source or PGT-A status; doing so with this data would produce figures that look more precise than the underlying records justify.
- Per-transfer, not cumulative. All rates are per transfer. A cumulative per-patient live birth rate cannot be derived here – the register records pregnancy test outcomes, not deliveries.
- Register inconsistencies. Three transfers have no PGT-A entry, four have indeterminate donor status, and one patient (P35) has a second, empty transfer row. These gaps are small in number but should be closed at source.
- ERA hours are protocol-dependent. For a receptive result, the recommended hour reproduces the biopsy protocol exactly, so the modal 127 h describes clinic practice, not patient biology. Only the 8 displaced results carry independent information.

- ERA technical failure rate. Five of 40 reports (12.5%) were non-informative, invalid, or had insufficient RNA, exceeding the manufacturer’s quoted rate. This warrants review of biopsy and sample-handling technique.
- EMMA detects bacterial DNA, not viable infection. A positive result indicates DNA above a reference threshold; it does not establish active infection or causation, and no histological or hysteroscopic confirmation of chronic endometritis was available.^{6,8}
- Timing of tests relative to transfer was not recorded. Whether each ERA/EMMA result preceded or followed a given transfer, and whether detected organisms were treated before transfer, cannot be determined from the records supplied. Outcomes are therefore not linked to test results anywhere in this report.
- No control or comparison group. This is a descriptive single-cohort audit, not a controlled comparison. No causal inference should be drawn from any figure in it.

Conclusions

Across 66 cryopreserved embryo transfers in 35 patients, 39.7% of transfers with a recorded outcome resulted in a positive pregnancy test, and 24.1% resulted in a clinical pregnancy. The programme is predominantly a donor-oocyte and PGT-A-screened one: 56% of transfers used donor oocytes and 80% used embryos reported euploid.

Two findings warrant further investigation. First, the proportion of positive tests that were biochemical – 9 of 23, or 39% – is high for a euploid-embryo cohort and is the single most useful signal in this dataset. Second, the data-capture gaps described in Section 8, while individually minor, systematically undermine any attempt at stratified analysis. Recording donor status and PGT-A result against the transfer rather than the patient would allow the next review to report outcomes by oocyte source and testing status, which is where the clinically actionable comparisons lie.

The ERA and EMMA data add two further points. Approximately one in five women had a displaced window of implantation, which is the real yield of receptivity testing; this should be weighed against randomized evidence that routine receptivity-guided timing does not improve live birth rates.^{3,5} *Gardnerella vaginalis* was present in more than a quarter of women tested and rarely alone, indicating that endometrial dysbiosis in this population is typically polymicrobial and consistent with the non-Lactobacillus-dominated profiles associated with poorer reproductive outcome.^{6,8} The two tests showed no relationship to each other and should be interpreted as independent sources of information rather than combined into a single assessment.

Declarations

Ethics and data statement: This retrospective audit used routinely collected clinical data. All patient identifiers were removed prior to analysis; patients are reported by sequential codes and oocyte donors by pseudonymous codes, and the re-identification key is held separately by the clinic.

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Conflict of Interest: The authors declare no competing interests. ERA and EMMA/ALICE are proprietary assays performed by Igenomix.

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Appendix A – Per-patient detail

All 66 transfers by patient, in source-register order. Format: date · PGT-A status / pregnancy outcome.

Table A1. Transfer-level detail for all 35 patients. “Mixed” denotes one PGT-A-tested and one untested embryo transferred together. Codes P01-P35 and D01-D21 are pseudonyms assigned for this document; the re-identification key is held separately.

Patient	n	Transfers (date · PGT-A / outcome)	Oocyte donor
P01	1	15.06.26 Normal / Yes	Yes (D01)
P02	1	06.04.26 Normal / No	No
P03	1	22.04.26 Normal / Yes	No
P04	1	02.03.26 Normal / Yes	Yes (D02)
P05	2	04.12.25 No PGT / No; 24.04.26 No PGT / No	Yes (D03)
P06	1	13.03.26 Normal / Biochemical	No
P07	3	08.10.25 Normal / No; 24.06.26 Normal / Biochem; 28.07.26 No PGT / pending	No
P08	2	17.03.26 Normal / Biochem; 15.06.26 Normal / Yes	No
P09	2	07.11.25 Normal / No; 17.02.26 Normal / Yes	Yes (D04)
P10	2	18.07.24 Normal / No; 02.03.26 Normal / Yes	No
P11	1	20.10.25 Normal / No result	No
P12	2	25.11.25 Normal / No; 25.03.26 Normal / Yes	Yes (D01)
P13	1	24.11.25 Normal / No	No
P14	2	05.08.25 Normal / No; 05.11.25 Normal / No	Yes (D05)
P15	2	13.01.26 Normal / no result; 29.05.26 Normal / No	Yes (D06)
P16	2	15.05.26 Normal / No; 05.08.26 pending (no AH/AI)	No
P17	3	10.07.25 Normal / No; 23.03.26 pending; 20.04.26 Normal / Yes	Yes (D07, OPU 27.01.26)
P18	3	27.09.24 mixed / No; 04.11.24 mixed / No; 06.08.26 pending	Yes (D08)
P19	1	23.04.26 mixed (1 PGT + 1 no PGT) / Biochem	Yes (D09)
P20	2	30.01.26 Normal / Biochem; 22.06.26 Normal / Yes	Yes (D10)
P21	2	31.12.25 Normal / No; 15.04.26 Normal / Yes	Yes (D11)
P22	2	21.01.26 Normal / No; 14.04.26 Normal / Yes	Yes (D12)
P23	2	24.06.26 Normal / No; 27.07.26 Normal / pending	No
P24	3	17.10.24, 06.01.26, 01.06.26 – all Normal / all No	Yes (D13, D14)
P25	3	16.01.26 Normal / No; 23.03.26 mixed / No; 14.07.26 Normal / Yes	Yes (D15)
P26	3	27.01.26 Normal / Biochem; 02.03.26 Normal / No; 15.06.26 Normal / No	No
P27	2	21.03.26 Normal / No; 17.07.26 Normal / Biochem	Yes (D16)
P28	2	08.12.25 Normal / Biochem; 05.03.26 No PGT / No	Yes (D17)
P29	1	28.07.26 Normal / pending	No

Patient	n	Transfers (date · PGT-A / outcome)	Oocyte donor
P30	2	16.01.26 Normal / No; 30.06.26 Normal / Yes	No
P31	2	23.01.26 Normal / No; 14.05.26 Normal / Yes	No
P32	3	30.07.24 mixed / No; 21.11.24 mixed / No; 31.10.25 Normal / No	Yes (D18, D19, D20)
P33	1	26.02.24 Normal / No	No
P34	2	21.07.25 Normal / Biochem; 23.01.26 Normal / No	Yes (D21)
P35	1	04.05.26 Normal / No (second row exists but is empty)	No

Appendix B – ERA and EMMA results by patient

Codes P01-P35 match the transfer cohort in Appendix A. Codes X36-X40 are women with ERA/EMMA results but no transfer recorded in the cycle register.

Table B1. Combined ERA and EMMA results, 40 ERA reports and 36 EMMA reports. “-” indicates no numeric hour was issued. P04, P09, P18 and X36 have an ERA report but no EMMA report.

Patient	ERA verdict	Hour	Organisms detected (EMMA)
P01	Receptive	127 h	Atopobium vaginae, Bifidobacterium spp, Gardnerella vaginalis, Sneathia spp
P02	Receptive	127 h	None detected
P03	Late receptive	115 h	Bifidobacterium spp, Gardnerella vaginalis
P04	Late receptive	125 h	No EMMA report
P05	Non-informative	-	None detected
P06	Receptive	120 h	None detected
P07	Receptive	127 h	Bifidobacterium spp, Gardnerella vaginalis, Ureaplasma urealyticum
P08	Late receptive	115 h	None detected
P09	Receptive	P+6	No EMMA report
P10	Receptive	127 h	None detected
P11	Receptive	125 h	None detected
P12	Receptive	120 h	Bifidobacterium spp, Escherichia coli, Klebsiella pneumoniae, Streptococcus agalactiae
P13	Receptive	126 h	Gardnerella vaginalis
P14	Receptive	127 h	Ureaplasma urealyticum
P15	Insufficient RNA	-	None detected
P16	Receptive	127 h	None detected
P17	Invalid RNA	-	Bifidobacterium spp, Gardnerella vaginalis
P18	Receptive	P+5	No EMMA report
P19	Receptive	127 h	Bifidobacterium spp
P20	Receptive	127 h	Bifidobacterium spp, Gardnerella vaginalis

Patient	ERA verdict	Hour	Organisms detected (EMMA)
P21	Pre-receptive	-	None detected
P22	Receptive	126 h	Bifidobacterium spp
P23	Receptive	126 h	None detected
P24	Receptive	126 h	Ureaplasma urealyticum
P25	Receptive	126 h	None detected
P26	Receptive	127 h	Bifidobacterium spp, Gardnerella vaginalis, Mobiluncus spp, Mycoplasma hominis, Sneathia spp, Ureaplasma urealyticum
P27	Pre-receptive	152 h	Bifidobacterium spp, Streptococcus agalactiae
P28	Late receptive	113 h	Gardnerella vaginalis
P29	Pre-receptive	-	None detected
P30	Receptive	126 h	None detected
P31	Late receptive	114 h	None detected
P32	Non-informative	-	Ureaplasma urealyticum
P33	Receptive	128 h	None detected
P34	Receptive	120 h	Atopobium vaginae, Bifidobacterium spp, Fusobacterium nucleatum, Gardnerella vaginalis, Prevotella bivia, Prevotella disiens
P35	Receptive	121 h	None detected
X36	Receptive	122 h	No EMMA report
X37	Receptive	126 h	Atopobium vaginae, Bifidobacterium spp, Gardnerella vaginalis
X38	Receptive	120 h	None detected
X39	Receptive	126 h	None detected
X40	Invalid RNA	-	None detected

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 მოღვაწე 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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Research Article

ENDOMETRIAL MICROBIOME AND
RECURRENT IMPLANTATION FAILURE AFTER
TRANSFER OF PGT-A EUPLOID EMBRYOS:
IS THERE A MISSING LINK?

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ABSTRACT

Background: Recurrent implantation failure (RIF) remains a challenging problem in assisted reproductive technology (ART). The increasing use of preimplantation genetic testing for aneuploidy (PGT-A) has reduced the contribution of embryo aneuploidy to implantation failure after transfer of euploid blastocysts, increasing interest in maternal endometrial factors. Among these, endometrial receptivity, chronic endometritis, immune regulation, and the endometrial microbiome have received considerable attention. Molecular assays including Endometrial Receptivity Analysis (ERA), Endometrial Microbiome Metagenomic Analysis (EMMA), and Analysis of Infectious Chronic Endometritis (ALICE) have been proposed as tools for individualized evaluation, although their clinical utility remains uncertain.

Methods: A narrative review was conducted using evidence from peer-reviewed studies, systematic reviews, meta-analyses, randomized controlled trials, and contemporary recommendations from the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). Particular attention was given to evidence concerning endometrial microbiota, chronic endometritis, endometrial receptivity, and outcomes following euploid embryo transfer.

Results: The endometrial microbiome is biologically plausible as a component of the implantation environment. Still, current evidence is heterogeneous and limited by low microbial biomass, sampling-related contamination, inconsistent sequencing methodologies, and the absence of standardized definitions of dysbiosis. Although associations between microbial composition and reproductive outcomes have been reported, causality has not been established. Randomized evidence does not support routine ERA-guided embryo transfer, and evidence for EMMA – or ALICE-guided treatment remains insufficient. Patients with repeated implantation failure following euploid embryo transfer represent an important under-studied population.

Conclusion

Current evidence does not support routine microbiome or receptivity testing in IVF. However, after comprehensive evaluation for established causes of implantation failure, selected pa-

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tients with repeated failure after PGT-A-confirmed euploid embryo transfer may be considered for individualized endometrial assessment, with appropriate counseling that the clinical utility of ERA, EMMA, and ALICE remains unproven. Prospective studies specifically enrolling this population are required.

Keywords: recurrent implantation failure; PGT-A; euploid embryo; endometrial microbiome; chronic endometritis; endometrial receptivity; embryo implantation

Introduction

Embryo implantation is a highly coordinated biological process requiring temporal and functional synchrony between embryonic development and the maternal endometrium. Despite major advances in ovarian stimulation, embryo culture, blastocyst selection, vitrification, and genetic testing, implantation remains an inefficient step of human reproduction. Successful implantation depends not only on embryonic developmental competence but also on endometrial decidualization, progesterone responsiveness, vascular remodeling, immune regulation, epithelial function, and embryo-endometrial communication.^{1,2}

Historically, embryo quality was considered one of the principal determinants of implantation. Embryonic aneuploidy is indeed strongly associated with implantation failure and early pregnancy loss, particularly with increasing maternal age. PGT-A has enabled the preferential selection of blastocysts without detected whole-chromosome aneuploidy, thereby changing the clinical interpretation of repeated implantation failure.^{3,4}

However, a euploid embryo is not synonymous with a universally competent embryo, and euploid embryo transfer does not guarantee implantation. Developmental competence may also be influenced by factors not assessed by conventional PGT-A, including mitochondrial function, epigenetic regulation, cellular metabolism, trophoblast competence, and biological limitations of embryo biopsy and chromosome testing.^{5,6} Consequently, implantation failure after repeated transfer of euploid embryos cannot be attributed exclusively to the embryo and raises important questions concerning maternal and endometrial factors.

The endometrium is a dynamic tissue that undergoes profound cyclic changes under endocrine regulation. Decidualization, extracellular matrix remodeling, vascular adaptation, epithelial transformation, immune cell recruitment, and molecular signaling create a transient environment that supports embryo attachment and invasion.^{7,8} The possibility that microorganisms may also participate in this environment has generated substantial interest.

The concept of an endometrial microbiome remains controversial. Molecular techniques, particularly 16S ribosomal RNA sequencing and metagenomic approaches, have detected bacterial DNA in endometrial samples. However, the endometrial environment is characterized by extremely low microbial biomass, making results particularly vulnerable to contamination and methodological differences.^{9,10}

Early studies suggested that a *Lactobacillus*-dominant microbial profile might be associated with improved reproductive outcomes, generating interest in microbiome-based diagnostics. Subsequent studies, however, have produced inconsistent results, and the biological significance of bacterial DNA detected in the uterine cavity remains incompletely defined.

This uncertainty has contributed to the development and clinical use of molecular assays such as ERA, EMMA, and ALICE. ERA evaluates transcriptomic markers associated with endometrial receptivity; EMMA characterizes microbial composition; and ALICE was developed to detect microorganisms associated with chronic endometritis.

The central question is therefore not whether these biological phenomena exist, but whether their assessment and treatment improve clinically meaningful reproductive outcomes.

This distinction is particularly relevant in patients with repeated implantation failure after transfer of PGT-A-confirmed euploid embryos. These patients represent a highly selected population in whom one major contributor to implantation failure—embryonic aneuploidy—has been substantially reduced, although not eliminated. Yet this population remains underrepresented in clinical trials of molecular endometrial diagnostics.

The objective of this review is to critically evaluate the evidence linking the endometrial microbiome with RIF after euploid embryo transfer, examine the clinical evidence for ERA, EMMA, and ALICE, and consider whether integrated endometrial assessment may have a role in carefully selected patients.

Recurrent Implantation Failure After Euploid Embryo Transfer

There is no universally accepted definition of RIF. ESHRE has emphasized that RIF should be interpreted individually, taking into account the patient's probability of implantation rather than relying solely on a fixed number of failed transfers.¹ The recently published ASRM committee opinion similarly emphasizes individualized assessment of patients with repeated unsuccessful embryo transfers.¹⁴

This distinction is important because the probability of implantation varies according to maternal age, embryo quality, embryo developmental stage, number of embryos transferred, laboratory performance, and other clinical factors.

Transfer of a PGT-A-confirmed euploid embryo reduces the probability that whole-chromosome aneuploidy is responsible for a failed transfer. However, PGT-A does not measure all components of embryonic competence. Mosaicism, limitations of trophectoderm biopsy, mitochondrial function, epigenetic regulation, and developmental competence remain relevant biological variables.^{5,6}

Consequently, repeated failure after euploid embryo transfer should not automatically be interpreted as evidence of an endometrial abnormality. Nevertheless, when several good-quality euploid embryos fail to implant, systematic reassessment of both embryo-related and maternal factors becomes increasingly reasonable.

The first step should remain evaluation of established causes of implantation failure. These include uterine cavity abnormalities, untreated hydrosalpinx, clinically significant adenomyosis or endometriosis when relevant, endocrine disorders, and other patient-specific factors.^{1,14}

Only after such factors have been considered should less well-validated molecular or microbiological investigations be discussed.

The Endometrial Microbiome: Biological Plausibility and Methodological Challenges

The discovery of bacterial DNA in endometrial samples challenged the traditional concept of a sterile uterine cavity. However, the presence of microbial DNA does not necessarily demonstrate the presence of a stable, metabolically active microbial community.

The endometrium is a low-biomass environment. This creates a methodological problem that is considerably less pronounced in high-biomass environments such as the vagina or gastrointestinal tract. During transcervical sampling, bacterial DNA from the vagina, cervix, instruments, reagents, extraction kits, or laboratory environment may influence sequencing results.^{9,10}

Therefore, interpretation of endometrial microbiome studies requires particular attention to negative controls, sampling methodology, sequencing platforms, bioinformatic pipelines, and the distinction between true biological signals and contamination.

Early studies proposed that *Lactobacillus*-dominant endometrial communities were associated with improved implantation and pregnancy outcomes.¹¹ However, subsequent investigations have not consistently reproduced this association. ESHRE specifically notes that studies examining the relationship between *Lactobacillus* abundance and implantation have produced conflicting findings and that the clinical relevance of uterine and vaginal microbiome profiling remains uncertain.¹ This inconsistency suggests that microbial composition alone may be an insufficient measure of endometrial health.

The functional characteristics of microbial communities may be more relevant than the relative abundance of individual taxa. Microbial metabolites, host-microbe interactions, immune signaling, epithelial integrity, and local inflammatory responses may all influence the biological environment in which implantation occurs.

At present, however, evidence supporting these mechanisms remains predominantly observational or experimental. The critical unanswered question is whether a particular microbial abnormality causes implantation failure or simply reflects another underlying alteration of the endometrium.

This distinction has direct clinical implications. If dysbiosis is causal, correcting it could theoretically improve implantation. If dysbiosis is instead a consequence of, or a marker for, another endometrial disorder, microbial manipulation alone may not improve reproductive outcomes. Therefore, detection of bacterial DNA should not automatically be equated with active infection or with an indication for antibiotic treatment.

Endometrial Microbiome and Implantation Biology

The biological hypothesis linking the microbiome to implantation is nevertheless compelling. Microorganisms and microbial products may interact with epithelial and immune cells through pattern-recognition receptors, including Toll-like receptors and nucleotide-binding oligomerization domain-like receptors. These pathways participate in the regulation of cytokines, chemokines, antimicrobial peptides, and other mediators of mucosal immunity.^{15,16}

The implantation process itself requires a carefully controlled inflammatory environment. Local immune activation is necessary for tissue remodeling and implantation, while excessive or persistent inflammation may interfere with decidualization and trophoblast invasion.^{7,8}

Microbial communities could theoretically influence this balance through direct interactions with epithelial, immune, or stromal cells and through the production of metabolites. Lactate and other microbial metabolites may have biological effects on local cellular metabolism and immune signaling.

However, much of this mechanistic evidence does not specifically demonstrate a causal relationship between endometrial dysbiosis and implantation failure in humans.

Furthermore, the microbiome is not independent of the hormonal and anatomical environment. Progesterone exposure, estrogenic stimulation, menstruation, antibiotic use, sexual activity, uterine instrumentation, and the local inflammatory environment may all influence microbial composition.

Therefore, the microbiome may represent one component of a broader endometrial ecosystem rather than an isolated pathological entity.

ERA: Biological Rationale Versus Clinical Utility

Endometrial Receptivity Analysis was developed on the premise that the timing of endometrial receptivity may vary among women and that a displaced implantation window could contribute to implantation failure.

ERA uses transcriptomic analysis of endometrial tissue to classify the endometrium's molecular state and potentially personalize the timing of embryo transfer.^{17,18} The biological hypothesis is attractive: if a patient's endometrium is not synchronized with embryo development, adjustment of progesterone exposure could theoretically improve implantation.

Initial observational studies generated considerable interest. However, subsequent randomized evidence has not demonstrated a consistent improvement in live birth with ERA-guided embryo transfer.

A major randomized clinical trial published in JAMA compared endometrial receptivity testing-guided timing with standard timing of frozen embryo transfer and found no significant improvement in live birth.¹⁹

More recent evidence, therefore, does not support the routine use of ERA as a universal diagnostic test.

The negative randomized evidence should not be interpreted as proof that transcriptomic receptivity has no biological significance. Rather, it demonstrates that identifying a transcriptomic state and modifying transfer timing based on it has not consistently been shown to improve live birth.

Several explanations are possible. Endometrial receptivity is not a single molecular event but a complex and dynamic process. A single biopsy may not completely represent biological variation between cycles, and transcriptomic signatures may capture only one component of implantation competence.

Importantly, most ERA trials have not been specifically designed around patients with repeated failure following transfer of multiple PGT-A-confirmed euploid embryos. Therefore, whether a highly selected euploid-RIF population could derive a different degree of benefit remains uncertain.

Current ASRM guidance recognizes the conflicting evidence surrounding ERA and does not support routine endometrial receptivity testing as standard care for RIF.¹⁴

Accordingly, ERA should currently be regarded as an investigational or selectively considered assessment rather than a validated intervention capable of improving live birth in routine IVF.

EMMA and ALICE: What Do They Actually Tell Us?

EMMA and ALICE address different biological questions and should not be interpreted as interchangeable tests.

EMMA is intended to characterize the microbial composition of the endometrial cavity. Its clinical premise is that a particular microbial profile, especially one dominated by *Lactobacillus* species, may be associated with a more favorable implantation environment.

ALICE is intended to identify microorganisms associated with chronic endometritis.

This distinction is clinically important because microbiome composition and chronic endometritis are not synonymous.

A patient may have bacterial DNA detected without histological evidence of chronic endometrial inflammation. Conversely, chronic endometritis may be diagnosed by the identification of plasma cells, despite uncertainty about the specific microbial cause.

The principal limitation of EMMA is the absence of a universally validated definition of a 'normal' endometrial microbiome. A fixed threshold of *Lactobacillus* abundance should therefore not be interpreted as an established biological cutoff capable of predicting implantation or live birth.

Similarly, a positive ALICE result should not automatically be interpreted as proof of clinically significant infection requiring antimicrobial treatment.

Molecular assays detect nucleic acids. They do not necessarily establish bacterial viability, tissue invasion, or causality.

ESHRE currently states that uterine and vaginal microbiome profiling is not routinely recommended in RIF because important questions regarding sampling, reproducibility, spontaneous changes in the microbiota, and treatment efficacy remain unanswered.¹

This is an important distinction from the question of whether microbiome research should continue. The evidence is insufficient for routine clinical implementation, but the hypothesis remains scientifically relevant.

Chronic Endometritis: A Different Clinical Question

Chronic endometritis warrants separate consideration, as it is not equivalent to microbiome profiling.

Chronic endometritis is generally characterized by the presence of endometrial stromal plasma cells and may be assessed using histological examination with or without CD138 immunohistochemistry. However, diagnostic thresholds remain inconsistent between studies.^{14,20}

The prevalence of chronic endometritis varies substantially depending on the population studied and the diagnostic method used.

Some observational studies have reported improved reproductive outcomes following treatment of chronic endometritis, particularly when eradication is documented. However, these studies are predominantly observational and are affected by heterogeneous diagnostic criteria, antibiotic regimens, and patient populations.^{21,22}

A 2022 systematic review and meta-analysis reported better reproductive outcomes among patients in whom chronic endometritis was considered cured compared with those with persistent disease. Still, they emphasized important limitations of the available evidence.²³

The recently published 2026 ASRM RIF committee opinion recognizes chronic endometritis as a potentially relevant consideration in RIF while emphasizing the lack of standardized diagnostic criteria and the limitations of the evidence.¹⁴

Therefore, in a patient with repeated implantation failure after euploid embryo transfer, evaluation for chronic endometritis may be clinically reasonable when appropriately indicated. Still, it should not be equated with routine microbiome testing.

Importantly, treatment decisions should be based on a clinically meaningful diagnosis rather than solely on detection of bacterial DNA.

Should ERA, EMMA, and ALICE Be Tested in Patients With Repeated Euploid Implantation Failure?

This question requires a distinction between routine testing and selective investigation.

Current evidence does not support routine ERA, EMMA, or ALICE testing for all IVF patients. ESHRE explicitly recommends against routine uterine and vaginal microbiome profiling in RIF, and ASRM's 2026 RIF guidance remains cautious regarding endometrial receptivity testing and microbiome-based diagnostics.^{1,14}

However, the population of women experiencing repeated implantation failure after transfer of multiple PGT-A-confirmed euploid embryos has not been adequately studied.

This creates an important evidence gap.

A patient with one failed euploid embryo transfer should not automatically be considered to have an endometrial disorder. Even a euploid embryo can fail to implant for biological reasons that remain incompletely understood.

In contrast, after repeated failures with several good-quality euploid embryos, a clinician may reasonably reconsider whether additional maternal factors warrant investigation.

In such a patient, I would consider the following hierarchy:

1. Reassess embryo-related factors and the limitations of PGT-A.
2. Reassess uterine anatomy and cavity pathology.
3. Review endocrine and systemic factors.
4. Review the frozen embryo transfer protocol and luteal support.
5. Consider clinically indicated assessment for chronic endometritis.
6. Only after comprehensive evaluation, discuss the potential role of molecular endometrial tests such as ERA, EMMA, or ALICE.
7. Provide explicit counseling that the clinical benefit of these tests remains unproven.

This approach avoids both extremes: indiscriminate testing of all IVF patients and complete dismissal of potentially informative investigations in exceptionally selected cases.

The critical principle is that testing should not automatically lead to treatment.

An abnormal EMMA or ALICE result should not, by itself, mandate antibiotics or probiotics. Similarly, an ERA result should not automatically be assumed to identify the correct timing of embryo transfer in a way that improves live birth.

From Individual Biomarkers to Integrated Endometrial Assessment

The limitations of individual tests may reflect the biological complexity of implantation itself. ERA evaluates transcriptomic receptivity. EMMA evaluates microbial composition. ALICE attempts to identify microorganisms associated with chronic endometritis. Histopathology evaluates inflammatory cellular changes. Ultrasound and hysteroscopy assess anatomical factors. Each test interrogates a different component of the endometrium.

Implantation, however, is an integrated process.

A useful conceptual framework would therefore combine four domains:

1. Endometrial receptivity

This includes progesterone-dependent transcriptomic maturation and synchronization between embryo development and the endometrial cycle.

2. Microbial homeostasis

This includes microbial composition, diversity, functional activity, and the methodological reliability of microbial detection.

3. Inflammatory and immune status

This includes chronic endometritis, local inflammatory pathways, and clinically meaningful immune abnormalities.

4. Clinical and embryological context

This includes maternal age, infertility diagnosis, uterine anatomy, embryo morphology and developmental kinetics, PGT-A results, previous transfer outcomes, endocrine status, and treatment protocol.

The concept of integrated functional endometrial assessment is therefore biologically attractive. However, it is important to emphasize that this is a research framework, not a validated clinical algorithm.

No randomized controlled trial has yet demonstrated that combining ERA, EMMA, ALICE, histopathological assessment, and individualized treatment improves live birth in women with repeated implantation failure after transfer of euploid embryos.

Consequently, this framework should not be presented as an established standard of care.

Current Evidence From Professional Societies

The recommendations of professional societies are particularly important because commercial availability of a diagnostic test does not constitute evidence of clinical validity.

ESHRE's 2023 good-practice recommendations emphasize that RIF is heterogeneous and that many investigations used in clinical practice lack sufficient evidence of benefit. Specifically, uterine and vaginal microbiome profiling is currently not recommended because the clinical relevance, optimal sampling methodology, stability of microbiome profiles, and effectiveness of interventions remain uncertain.¹

The 2026 ASRM committee opinion similarly takes a cautious approach. It discusses the conflicting evidence for ERA and emphasizes that additional evidence is required before routine screening and treatment based on microbiome findings can be recommended.¹⁴

These recommendations should not be interpreted as a rejection of the underlying biology. Rather, they illustrate an essential principle of evidence-based medicine: a plausible biological mechanism is not sufficient to establish clinical utility.

The appropriate question is whether a diagnostic test followed by a specific intervention improves outcomes that matter to patients, particularly live birth.

Discussion

The endometrial microbiome represents one of the most intriguing potential contributors to implantation biology, but the current evidence does not justify describing it as an established cause of RIF.

Several observations support continued investigation. Microbial DNA can be detected in endometrial samples; microorganisms and microbial products can interact with host immune and epithelial pathways; and associations between microbial profiles and reproductive outcomes have been reported.⁹⁻¹³

At the same time, important limitations remain.

The endometrium is a low-biomass environment, and contamination can substantially affect sequencing results. Different studies use different sampling methods, sequencing technologies, bioinformatic approaches, and definitions of dysbiosis. Furthermore, the presence of bacterial DNA does not establish viability or pathogenicity.

The concept of *Lactobacillus* dominance is similarly more complex than initially proposed. Although *Lactobacillus* species have an established role in the vaginal microbiome, a specific *Lactobacillus* threshold cannot currently be regarded as a validated predictor of implantation or live birth in the endometrium.¹

The euploid-RIF population is particularly interesting because embryonic aneuploidy has been substantially reduced as an explanation for repeated failed transfers. Nevertheless, this does not establish that endometrial abnormalities are responsible.

This distinction is crucial.

It is scientifically reasonable to hypothesize that maternal factors may contribute more strongly when repeated euploid embryo transfers fail. It is not scientifically justified to conclude that a positive microbiome test identifies the cause of implantation failure.

The same reasoning applies to ERA. Transcriptomic differences are biologically meaningful, but randomized evidence does not demonstrate that changing embryo transfer timing according to ERA improves live birth.¹⁹

Therefore, the most defensible position is neither enthusiastic adoption nor complete dismissal. In routine IVF practice, current evidence does not support universal testing for ERA, EMMA, or ALICE.

For carefully selected patients with repeated implantation failure after multiple PGT-A-confirmed euploid embryo transfers, however, discussion of these investigations may be reasonable once conventional evaluation is complete and the patient understands that their clinical utility remains uncertain.

This is particularly true for chronic endometritis, where contemporary evidence and ASRM guidance provide a stronger clinical rationale for consideration of diagnostic evaluation than for microbiome profiling itself.^{14,23}

The distinction between testing and treatment is also fundamental.

A molecular abnormality should not automatically result in antibiotic therapy, probiotic administration, or alteration of progesterone exposure. Such interventions require their own evidence base.

The ultimate objective should therefore not be to identify the largest number of molecular abnormalities. It should be to identify abnormalities that are reproducible, biologically meaningful, causally related to implantation failure, and therapeutically modifiable.

Limitations

This review has several limitations.

First, it is a narrative review rather than a systematic review or meta-analysis and may therefore be affected by selection of literature.

Second, the available evidence concerning the endometrial microbiome is heterogeneous, particularly with respect to sampling techniques, microbial biomass, sequencing methodology, and diagnostic definitions.

Third, randomized trials specifically investigating patients with repeated implantation failure after transfer of PGT-A-confirmed euploid embryos remain limited.

Fourth, many studies examining ERA, EMMA, ALICE, and chronic endometritis include heterogeneous IVF populations, making direct extrapolation to euploid-RIF patients uncertain.

Finally, the proposed concept of integrated endometrial assessment remains hypothetical and should not be interpreted as a validated clinical pathway.

Future Research Priorities

Future studies should specifically enroll patients with repeated implantation failure after transfer of PGT-A-confirmed euploid embryos rather than combining them with heterogeneous IVF populations.

Research priorities should include:

1. **Standardization of microbiome sampling**, including rigorous contamination controls and reproducible laboratory protocols.
2. **Functional microbiome characterization**, moving beyond simple taxonomic abundance toward metagenomics, meta-transcriptomics, metabolomics, and strain-level analysis.
3. **Standardized definitions of chronic endometritis**, including reproducible histological and immunohistochemical criteria.
4. **Prospective evaluation of ERA**, specifically in patients with repeated euploid embryo-transfer failure.
5. **Prospective evaluation of EMMA and ALICE**, with predefined diagnostic thresholds and clinically meaningful treatment algorithms.
6. **Randomized controlled trials of test-directed treatment**, rather than observational studies reporting outcomes after treatment.

7. **Integration of molecular and clinical phenotypes**, including transcriptomics, microbiome data, immune profiling, progesterone responsiveness, decidualization, and embryo characteristics.
8. **Use of cumulative live birth as the principal endpoint**, rather than implantation rate or biochemical pregnancy alone.

The most important future study would be a prospective, multicenter randomized trial enrolling women with repeated implantation failure after transfer of PGT-A-confirmed euploid embryos and comparing standard evaluation with a predefined integrated endometrial diagnostic and treatment strategy.

Such a study could determine whether molecular endometrial testing has clinical value in the population in which its biological rationale is strongest.

Conclusion

The endometrial microbiome is a biologically plausible component of the maternal environment in which implantation occurs. However, current evidence does not establish endometrial dysbiosis as an independent, causal, and therapeutically modifiable cause of recurrent implantation failure.

PGT-A has reduced, but not eliminated, the contribution of embryonic chromosomal abnormalities to implantation failure. Repeated failure after transfer of multiple PGT-A-confirmed euploid embryos therefore represents an important clinical scenario in which maternal factors deserve careful reassessment.

Current evidence does not support routine use of ERA, EMMA, or ALICE in IVF. Randomized evidence has not demonstrated consistent improvement in live birth with ERA-guided embryo transfer, while evidence supporting microbiome-guided interventions remains insufficient.^{1,14,19} Nevertheless, the absence of evidence for routine use should not be interpreted as proof that these technologies have no value in every patient. Women with repeated implantation failure after multiple euploid embryo transfers remain underrepresented in clinical trials and may represent a biologically distinct population.

After comprehensive assessment of established anatomical, endocrine, embryological, and systemic factors, selective evaluation of the endometrium may be considered in carefully counseled patients. Evaluation for chronic endometritis currently has a stronger clinical rationale than routine microbiome profiling. In contrast, ERA, EMMA, and ALICE should be regarded as complementary or investigational tools whose ability to improve live birth has not been proven. The future of reproductive medicine is unlikely to depend on a single biomarker. The more promising direction is an integrated understanding of endometrial receptivity, microbial ecology, inflammation, immune regulation, endocrine responsiveness, decidualization, and embryonic competence.

The endometrial microbiome may ultimately prove to be part of the missing link in recurrent implantation failure after euploid embryo transfer. At present, however, it should be regarded as a promising biological hypothesis rather than an established clinical diagnosis.

Declaration

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Ethical Approval

Ethical approval was not required because this manuscript is a narrative review of previously published literature and does not involve human participants or identifiable patient data.

Author Contributions

Ana Aivazova was responsible for the manuscript conception, literature review, interpretation of the evidence, drafting, critical revision, and final approval of the submitted version.

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Research Article

AUTOLOGOUS ADIPOSE-DERIVED STEM CELL THERAPY FOR OVARIAN AND ENDOMETRIAL REGENERATION IN INFERTILE PATIENTS: A SINGLE-CENTER PILOT STUDY

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ABSTRACT

Background: Diminished ovarian reserve (DOR) and refractory thin endometrium present major therapeutic challenges in assisted reproductive technology (ART). Conventional treatments frequently yield suboptimal outcomes, prompting growing interest in regenerative strategies such as autologous adipose-derived stem cell (ADSC) transplantation. This study aimed to evaluate the clinical efficacy and safety of autologous ADSC transplantation for ovarian function and endometrial regeneration in infertile women with DOR or refractory endometrium undergoing ART.

Methods: In this retrospective, single-center pilot study conducted between July 2023 and January 2026 at a tertiary reproductive center in Tbilisi, Georgia, 25 infertile women were evaluated. Twenty patients with DOR who met the Bologna criteria received transvaginal ultrasound-guided intraovarian ADSC injection, and 5 patients with refractory thin endometrium (<7 mm) received intrauterine catheter-guided delivery. Patients with elevated malignancy markers (CA-125, HE4, or abnormal ROMA index) were excluded. Interventions involved minimally invasive lipoaspiration followed by enzymatic isolation of stromal vascular fraction (SVF) containing ADSCs. Primary outcomes included changes in antral follicle count (AFC), follicular development, and endometrial thickness (EMT). Secondary outcomes included restoration of trilaminar morphology, clinical pregnancy rates, and adverse events.

Results: The mean (SD) age was 40.0 (5.1) years in the ovarian cohort and 42.8 (5.4) years in the endometrial cohort. Following intraovarian ADSC transplantation, mean (SD) AFC increased significantly from 3.0 (2.6) to 3.9 (2.7) ($P < 0.01$), and mean (SD) dominant follicle count improved from 0.4 (0.6) to 1.6 (0.8) ($P < 0.01$). In the endometrial cohort, mean (SD) EMT increased from 6.1 (1.3) mm to 7.5 (2.2) mm ($P = 0.62$), with trilaminar morphology restored in 3 of 5 patients (60%). One clinical pregnancy was achieved in the endometrial cohort, and one ongoing pregnancy was documented in the ovarian cohort. No major procedural complications or serious adverse events occurred.

Conclusions: Autologous ADSC transplantation was associated with improved ovarian activity and enhanced endometrial development in selected infertile women with DOR or refractory thin

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endometrium. While these preliminary findings suggest ADSC therapy represents a promising adjunctive regenerative strategy in reproductive medicine, larger prospective randomized controlled studies are required to establish efficacy, long-term safety, and reproductive outcomes.

Keywords: adipose-derived stem cells; assisted reproductive technology; diminished ovarian reserve; infertility; in vitro fertilization (IVF); regenerative medicine; thin endometrium.

Introduction

Infertility affects approximately 10% to 15% of reproductive-aged couples worldwide and represents a major public health concern with substantial medical, psychological, and socioeconomic consequences.¹ Despite significant advances in assisted reproductive technology (ART), diminished ovarian reserve (DOR) and refractory thin endometrium remain among the most challenging conditions encountered in reproductive medicine because both are associated with poor ovarian response, implantation failure, and reduced live birth rates.^{2,3}

DOR is characterized by reduced quantity and quality of the oocyte pool, resulting in a poor response to controlled ovarian stimulation (COS). Although ovarian reserve decreases physiologically with age, DOR may also occur secondary to genetic abnormalities, previous ovarian surgery, chemotherapy, autoimmune disorders, or idiopathic causes. Women with DOR typically demonstrate reduced serum anti-Müllerian hormone (AMH) concentrations, decreased antral follicle count (AFC), and poor ovarian response during in vitro fertilization (IVF), ultimately resulting in lower pregnancy rates.^{2,4} Current therapeutic strategies, including individualized ovarian stimulation protocols, androgen supplementation, dehydroepiandrosterone (DHEA), coenzyme Q¹⁰, and platelet-rich plasma (PRP), have shown inconsistent efficacy, and no regenerative treatment has been universally adopted.⁵

Similarly, refractory thin endometrium remains an important cause of implantation failure in women undergoing ART. Although implantation depends on multiple factors, an endometrial thickness of less than 7 mm has consistently been associated with reduced implantation and pregnancy rates.³ Conventional therapies, including prolonged estrogen administration, vasoactive agents (e.g., sildenafil, pentoxifylline), granulocyte colony-stimulating factor (G-CSF), and intrauterine PRP, may improve endometrial development in selected patients; however, a subset of women remain resistant to these treatments and continue to experience repeated implantation failure.⁶

Regenerative medicine has emerged as a promising therapeutic strategy for reproductive disorders. Among mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs) have attracted considerable interest because of their abundance, ease of harvest, high proliferative capacity, and potent paracrine activity.^{7,8} Rather than directly replacing damaged tissue, ADSCs exert their regenerative effects primarily through secretion of cytokines, growth factors (including vascular endothelial growth factor [VEGF], transforming growth factor-beta [TGF- β], insulin-like growth factor [IGF]), and extracellular vesicles.^{8,9} These signaling molecules stimulate angiogenesis, modulate inflammation, reduce apoptosis, and recruit local progenitor cells to regenerate damaged stromal networks.⁹ Experimental studies have demonstrated that ADSCs may enhance ovarian vascularization, activate dormant follicles, improve granulosa cell survival, and promote endometrial regeneration by facilitating stromal remodeling and neovascularization.¹⁰⁻¹²

Early clinical investigations have reported encouraging improvements in ovarian reserve markers, follicular development, endometrial thickness, and pregnancy outcomes following stem-

cell-based therapies in women with DOR, premature ovarian insufficiency, and severe endometrial damage.^{10,13-20} However, current evidence remains limited by small sample sizes, heterogeneous patient populations, variable stem cell isolation protocols, and lack of adequately powered randomized controlled trials. Consequently, the efficacy, safety, optimal route of administration, and long-term reproductive outcomes of ADSC therapy have not yet been established.

This single-center retrospective pilot study aimed to evaluate the clinical outcomes of autologous ADSC transplantation in women with diminished ovarian reserve or refractory thin endometrium undergoing ART. We hypothesized that autologous ADSC therapy would be associated with improvements in ovarian function, follicular development, and endometrial regeneration while demonstrating an acceptable short-term safety profile.

Methods

Study Design and Patient Population

This retrospective, observational pilot study evaluated consecutive patients who underwent autologous ADSC transplantation at the Georgian-German Reproduction Center in Tbilisi, Georgia, between July 2023 and January 31, 2026. The study evaluated the clinical outcomes of autologous adipose-derived stem cell (ADSC) transplantation in women with diminished ovarian reserve (DOR) or refractory thin endometrium undergoing assisted reproductive treatment.

The study protocol adhered to the ethical principles of the Declaration of Helsinki. Institutional review was obtained, and all patients provided written informed consent prior to undergoing liposuction and cell transplantation.

Participant Selection and Cohort Allocation

Twenty-five women with infertility who underwent autologous ADSC transplantation during the study period were included.

Patients were allocated into 2 treatment groups according to their clinical indication:

- **Ovarian cohort (n = 20):** Women with DOR who underwent ultrasound-guided bilateral intraovarian ADSC transplantation.
- **Endometrial cohort (n = 5):** Women with refractory thin endometrium who underwent ultrasound-guided intrauterine ADSC catheterization.

Only consecutive patients meeting the predefined eligibility criteria during the study period were included in the analysis.

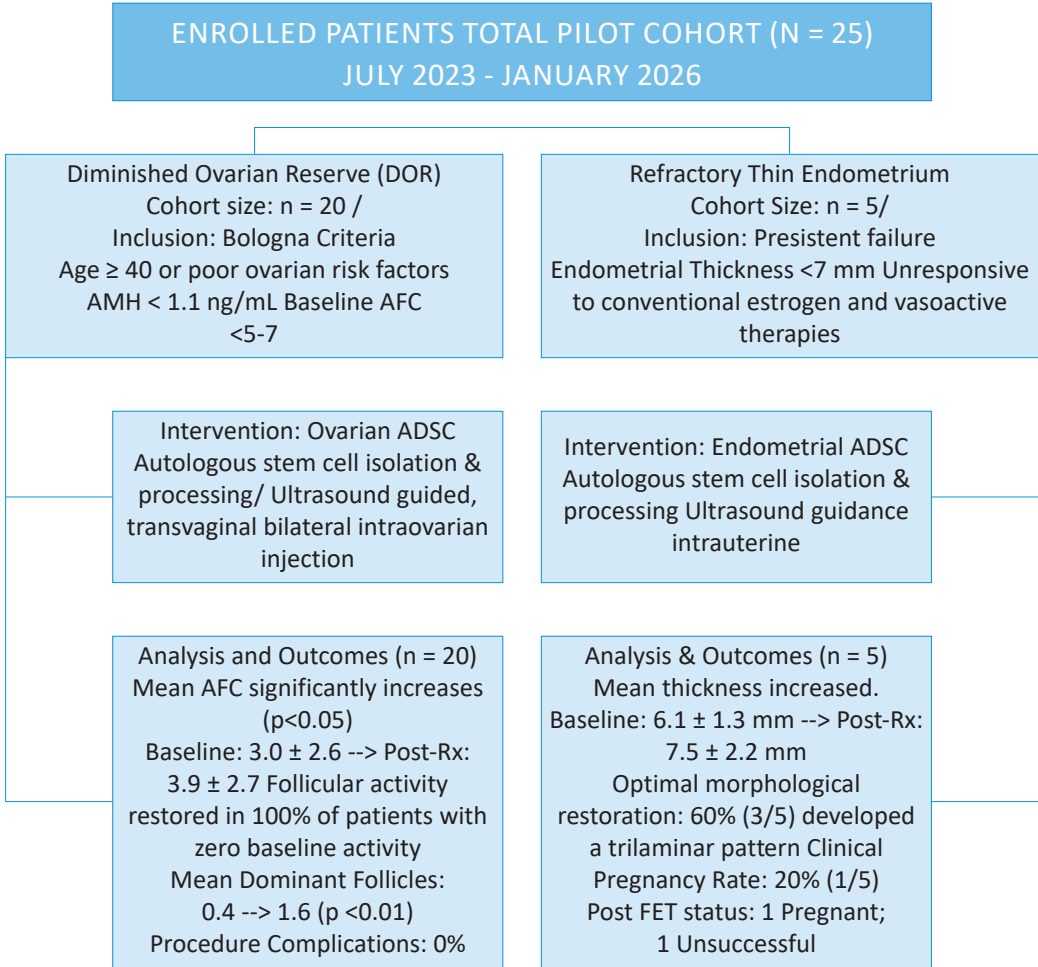


Figure 1. Patient selection and cohort allocation flowchart. A total of 25 patients met the strict selection criteria (Bologna criteria for the diminished ovarian reserve cohort; persistent endometrial thickness <7 mm for the endometrial cohort) and were analyzed for primary and secondary regenerative outcomes following autologous ADSC transplantation.

Inclusion and Exclusion Criteria

Inclusion Criteria (Ovarian Cohort): Must meet at least 2 Bologna criteria for poor ovarian response, including^{2:}

- maternal age ≥ 40 years or risk factors for poor ovarian response;
- serum anti-Mullerian hormone concentration <1.1 ng/mL;
- antral follicle count (AFC) <5-7 follicles;
- previous poor ovarian response during controlled ovarian stimulation (≤ 3 oocytes retrieved with conventional stimulation).

Inclusion Criteria (Endometrial Cohort): Persistent EMT < 7 mm on the trigger or progesterone introduction in at least two previous consecutive cycles, despite high-dose oral/vaginal estrogen therapy and ancillary treatments.

Exclusion Criteria

Patients were excluded if any of the following conditions were present:

- elevated ovarian malignancy markers;
- active malignancy;
- untreated endocrine disorders;
- severe endometriosis (stage III-IV);

- uterine structural abnormalities, including submucosal leiomyomas or intrauterine adhesions;
- active pelvic infection;
- contraindication to transvaginal or intrauterine intervention.

Before ADSC transplantation, all patients underwent malignancy risk assessment using serum cancer antigen 125 (CA-125), human epididymis protein 4 (HE4), and the Risk of Ovarian Malignancy Algorithm (ROMA) index. Patients with abnormal findings suggestive of increased ovarian malignancy risk were excluded from treatment.

ADSC Harvesting and Processing

Autologous adipose tissue (50-100 mL) was obtained using minimally invasive syringe lipoaspiration from the abdominal wall or gluteal region under sterile operating-room conditions. To isolate the unmanipulated stromal vascular fraction (SVF) containing resident adipose-derived stem cells (ADSCs), the harvested lipoaspirate was processed using a standardized, one-step digestion protocol as follows:

- **Washing:** The raw lipoaspirate was washed repeatedly with sterile phosphate-buffered saline (PBS) to remove systemic blood contamination, tumescent fluid, and free lipids.
- **Enzymatic Digestion:** The washed adipose tissue was subjected to enzymatic digestion using sterile collagenase. The mixture was incubated at 37°C for approximately 30-45 minutes with gentle, continuous agitation to break down the extracellular matrix.
- **Separation & Centrifugation:** To neutralize the enzyme, a sterile culture medium or saline solution was added. The digested mixture was then centrifuged to separate the mature, buoyant adipocytes and oil layer from the cellular pellet.
- **Filtration:** The supernatant (containing mature fat cells and liquid) was discarded, and the remaining cellular pellets, representing the heterogeneous stromal vascular fraction (SVF), were resuspended in sterile saline. To ensure safety and remove any remaining tissue fragments, the suspension was passed through a 100-µm mesh filter.
- **Quality Control:** Cell viability and absolute cell count of the final SVF suspension were determined using an automated cell counter via the trypan blue exclusion assay prior to clinical administration. A sterility test aliquot was also processed.

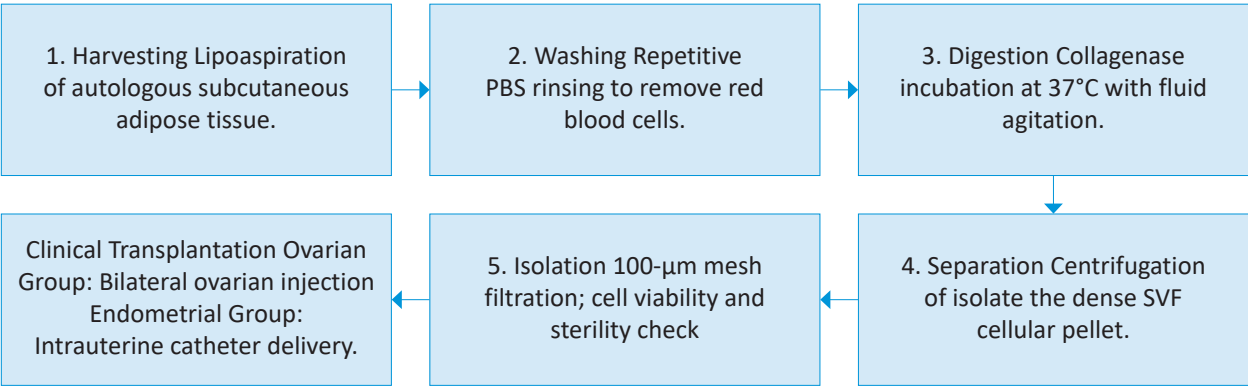


Figure 2. Schematic representation of autologous adipose-derived cell (ADSC) isolation and processing. The workflow illustrates the sequential steps from therapeutic lipoaspiration, mechanical and/or enzymatic processing via collagenase digestion, and gradient centrifugation to yield the cellular stromal vascular fraction (SVF) pellet, through definitive filtration quality control validation, to ultimate clinical autologous transplantation.

ADSC Administration Procedure

Ovarian ADSC Transplantation

Under conscious sedation, patients underwent transvaginal ultrasound-guided intraovarian injection of autologous ADSCs. A 17-gauge single-lumen aspiration needle was advanced into the ovarian stroma, and 1 to 2 mL of the prepared SVF suspension was slowly injected into each ovary. All procedures were performed by experienced reproductive medicine specialists using standard transvaginal ultrasound guidance.

Endometrial ADSC Administration

During the mid-proliferative phase of a preparation cycle, 1 to 2 mL of SVF suspension was gently instilled into the uterine cavity using a standard soft embryo transfer catheter under abdominal ultrasound guidance. Patients remained supine for 30 minutes following the procedure.

Outcome Measures

Primary Outcomes

- Primary outcome measures included:
- changes in AFC;
 - follicular development following ovarian stimulation;
 - change in endometrial thickness.

Secondary Outcomes

- Secondary outcome measures included:
- restoration of trilaminar endometrial morphology;
 - clinical pregnancy following embryo transfer;
 - procedure-related complications and adverse events.

Safety Assessment

Patients were monitored clinically following ADSC transplantation for procedure-related complications, including infection, bleeding, ovarian hyperstimulation syndrome, pelvic pain requiring hospitalization, and other adverse events.

No serious adverse events were observed during the study period.

Statistical Analysis

Continuous variables are presented as mean (SD) or median (IQR) based on normality. Pre- and post-treatment comparisons were performed using the paired t test for normally distributed variables and the Wilcoxon signed-rank test for nonnormally distributed variables. Categorical variables were compared using the Fisher exact test where appropriate. Two-sided P values < 0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 25 infertile women underwent autologous ADSC transplantation during the study period and were included in the final analysis. Twenty patients received intraovarian ADSC transplantation for diminished ovarian reserve, and 5 patients underwent intrauterine ADSC administration for refractory thin endometrium. No patients were excluded after treatment.

Baseline demographic and clinical characteristics are summarized in Table 1. The mean (SD) age of the patients in the ovarian cohort was 40.0 (5.1) years (range, 32-47 years), whereas the mean (SD) age in the endometrial cohort was 42.8 (5.4) years (range, 40-52 years). The ovarian cohort demonstrated a mean baseline AMH concentration of 0.21 (0.27) ng/mL and a mean baseline AFC of 3.0 (2.6) follicles. Patients in the endometrial cohort had a mean baseline endometrial thickness of 6.1 (1.3) mm and had experienced multiple previous unsuccessful ART cycles despite conventional treatment.

Ovarian Response Outcomes

Following intraovarian ADSC transplantation, patients showed significant improvements in ovarian reserve parameters and ovarian response during subsequent IVF cycles. The mean (SD) AFC rose from 3.0 (2.6) at baseline to 3.9 (2.7) post-treatment ($P < 0.01$). Furthermore, the mean (SD) number of dominant follicles developed during subsequent controlled ovarian stimulation increased from 0.4 (0.6) to 1.6 (0.8) ($P < 0.01$). Notably, one patient with complete bilateral absence of detectable follicles before treatment developed multiple follicles during subsequent ovarian stimulation following ADSC transplantation. Similar improvements in follicular recruitment were observed in additional poor responders. The mean AFC increased following treatment, and the mean number of dominant follicles also increased compared with baseline. These changes were accompanied by improved ovarian responsiveness during controlled ovarian stimulation. One ongoing clinical pregnancy was achieved in the ovarian treatment cohort. Detailed ovarian outcomes are presented in Table 2.

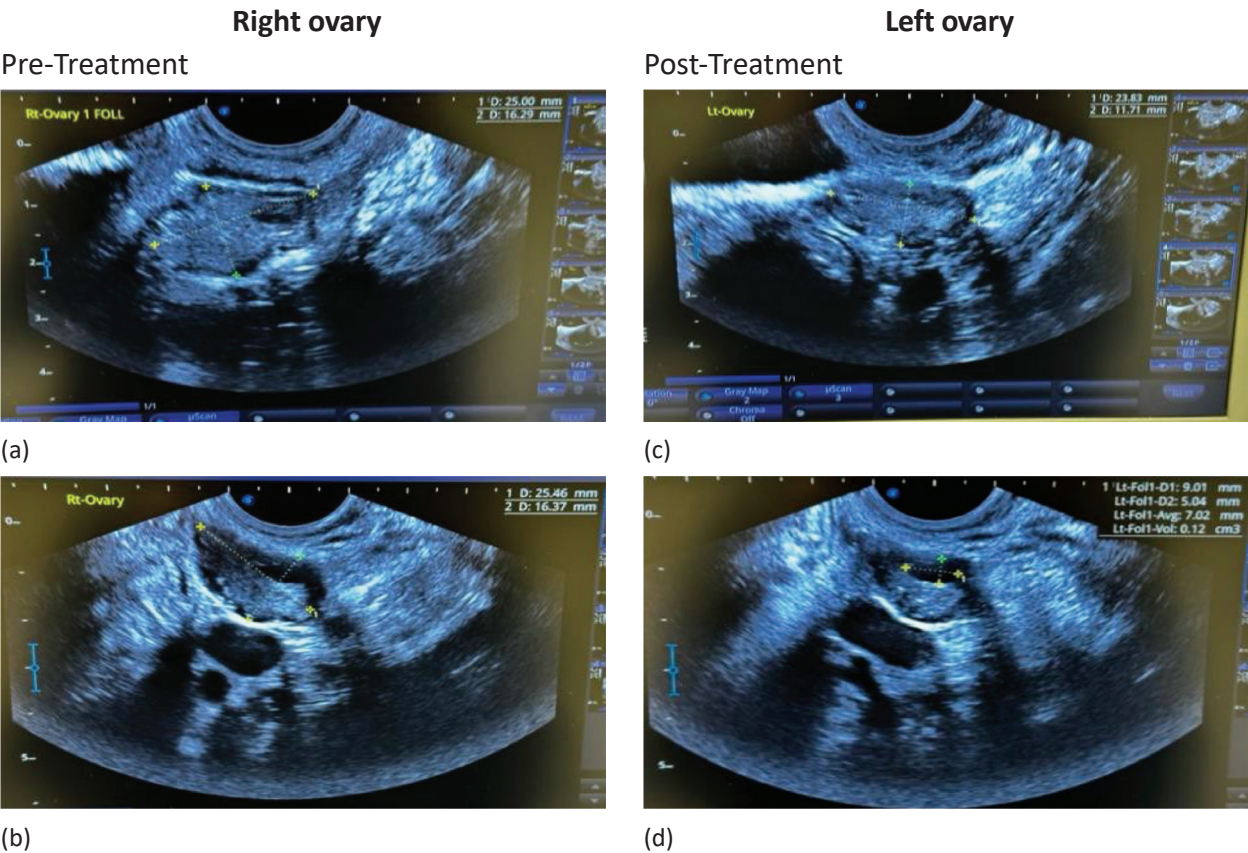


Figure 3. Transvaginal ultrasound monitoring of bilateral ovarian architecture pre- and post-autologous ADSC transplantation. (a) Baseline pre-treatment scan of the right ovary showing reduced follicular activity with a single small, restricted antral follicle. (b) Post-treatment evaluation of the right ovary showing persistence of the follicle with increased follicular size.

and maturation. (c) Baseline pre-treatment scan of the left ovary confirming absence of visible follicles with an absolute absence (0) of visible antral follicles. (d) Post-treatment evaluation of the left ovary documenting improved ovarian morphology with the appearance of a new antral follicle.

Endometrial Outcomes

Intrauterine ADSC therapy resulted in a mean (SD) EMT increase from 6.1 (1.3) mm before treatment to 7.5 (2.2) mm after treatment. Although this represented a clinically meaningful change that allowed embryo transfer to proceed, the increase did not reach statistical significance in this pilot sample (P = 0.62). Crucially, a favorable trilaminar pattern was restored in 3 of the 5 patients (60%), who previously lacked it. Following frozen embryo transfer (FET), one patient achieved a confirmed clinical pregnancy. One patient had a negative pregnancy test, and the remaining three patients were awaiting FET at the time of this analysis. Detailed endometrial outcomes are summarized in Table 3.

Table 3. Endometrial Outcomes Following ADSC Therapy.

Parameter	Pre-Treatment	Post-Treatment	p-value
Mean (SD) endometrial thickness, mm	6.1 (1.3)	7.5 (2.2)	0.62
Trilaminar Pattern Present, No. (%)	0/5 (0)	3/5 (60.0)	0.08
Clinical Pregnancies, No.	0	1	-

Safety and Adverse Events

No serious adverse events were reported following autologous ADSC transplantation. Specifically, no cases of pelvic infection, clinically significant bleeding, ovarian hyperstimulation syndrome (OHSS), or procedure-related complications were observed during the study period. Furthermore, no patients required hospital admission because of treatment-related adverse events. Safety outcomes are summarized in Table 4.

Table 4. Adverse Events and Safety Outcomes.

Complications	Frequency
Infection	0
Bleeding	0
Ovarian Hyperstimulation	0
Procedure-related complications	0

Discussion

This pilot study demonstrated that autologous ADSC transplantation is associated with improved ovarian activity and enhanced endometrial development in patients with severe DOR or refractory thin endometrium.^{10,13,14} The findings show a significant increase in AFC and dominant follicle recruitment, alongside improvements in late proliferative EMT and endometrial trilaminar morphology.

The therapeutic efficacy of ADSCs is likely mediated by their strong secretory profile rather than direct cellular differentiation.^{8,9} ADSCs release high concentrations of key cytokines and growth factors, including VEGF, TGF- β , basic fibroblast growth factor (bFGF), and hepatocyte growth factor (HGF).^{8,9} In the ovary, these paracrine mediators promote angiogenesis, reduce stromal apoptosis, and may rescue dormant primordial follicles.^{10,11} In the endometrium, these factors facilitate cellular proliferation, downregulate inflammatory pathways, and stimulate tissue remodeling, thereby resolving chronic fibrosis.^{14,19}

Our clinical findings align with early animal and human studies. Herraiz et al.¹⁰ demonstrated that mobilizing and transplanting bone marrow-derived stem cells could improve ovarian function in poor responders. Similarly, clinical trials by Tan et al.¹⁴ and other groups^{16,20} demonstrated that mesenchymal stem cell transplantation could repair damaged endometria and support successful clinical pregnancies. Our work extends these observations by utilizing ADSCs, which offer a more accessible cell source while maintaining strong therapeutic safety.

A key limitation of this study is its retrospective, noncontrolled design. Additionally, while the endometrial cohort showed a clinically meaningful increase in mean EMT from 6.1 mm to 7.5 mm, this did not reach statistical significance ($P = 0.62$) due to the small sample size ($n = 5$). Larger, prospective randomized controlled trials are required to confirm these findings, evaluate long-term live birth rates, and establish standardized processing and administration guidelines.

Conclusion

Autologous ADSC therapy may improve ovarian function and enhance endometrial receptivity in selected infertile patients with diminished ovarian reserve or refractory thin endometrium. These preliminary findings support the potential role of regenerative medicine approaches in assisted reproduction. Larger prospective randomized studies are required to confirm efficacy and establish standardized treatment protocols.

Declarations

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Conflict of Interest: The authors declare no competing interests.

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Research Article

IMPACT OF MATERNAL AGE ON EMBRYO CHROMOSOMAL COMPETENCE: A RETROSPECTIVE ANALYSIS OF 4,204 CONSECUTIVE PGT-A BLASTOCYSTS FROM A HIGH-VOLUME IVF CENTER

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ABSTRACT

Background: Maternal age is the most important determinant of embryo chromosomal competence and remains the strongest predictor of IVF success. Although preimplantation genetic testing for aneuploidy (PGT-A) has become an integral component of modern assisted reproductive technology (ART), large single-center studies evaluating comprehensive chromosomal outcomes across different maternal age groups remain relatively limited. Therefore, this study aimed to evaluate the association between maternal age and embryo chromosomal status in a large cohort of consecutive blastocysts analyzed by PGT-A.

Methods: This retrospective cohort study included 495 women undergoing IVF/ICSI with PGT-A between January 2025 and January 2026 at a high-volume IVF center. Patients were stratified into three maternal age groups: Group I, aged 20-29 years (n = 90); Group II, aged 30-39 years (n = 226); and Group III, aged 40-43 years (n = 179). Only patients with at least six biopsied blastocysts were included. A total of 4,204 blastocysts underwent trophectoderm biopsy followed by comprehensive chromosome screening using next-generation sequencing (NGS). The primary outcome was the proportion of euploid embryos. Secondary outcomes included the proportions of aneuploid, mosaic, and segmental-abnormality embryos, as well as samples yielding no result.

Results: Among the 4,204 blastocysts analyzed, 2,826 (67.2%) were euploid, 731 (17.4%) were aneuploid, 240 (5.7%) were mosaic, and 322 (7.7%) demonstrated segmental abnormalities; 85 (2.0%) yielded no result. Age-stratified analysis demonstrated a progressive decline in embryo euploidy with advancing maternal age, accompanied by increasing rates of chromosomal abnormalities.

Conclusions: Maternal age remains the strongest determinant of embryo chromosomal competence. Although high laboratory performance resulted in a very low technical failure rate, advancing maternal age was associated with reduced euploid embryo yield and increasing chromosomal abnormalities. These findings support individualized reproductive counseling and emphasize the clinical value of PGT-A in women of advanced reproductive age.

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Keywords: aneuploidy; blastocyst; embryo biopsy; euploidy; IVF; maternal age; mosaic embryo; PGT-A; segmental abnormality.

Introduction

Embryonic chromosomal abnormalities represent one of the leading causes of implantation failure, miscarriage, and reduced live birth rates following assisted reproductive technology (ART).^{1,3} Among all known prognostic factors, maternal age has consistently been identified as the strongest predictor of embryo chromosomal competence.^{3,4,7} Female reproductive aging is characterized by progressive deterioration in both the quantity and quality of oocytes.⁷ While declining ovarian reserve reduces the number of available oocytes, age-related impairment of oocyte competence has an even greater influence on reproductive success. The majority of chromosomal abnormalities originate during maternal meiosis, particularly during the first meiotic division, where cohesion loss, spindle instability, and impaired chromosome alignment increase the likelihood of nondisjunction.^{5,7,8} Consequently, embryos generated from older oocytes demonstrate substantially higher rates of whole-chromosome aneuploidy. Age-related deterioration of oocyte quality results primarily from meiotic spindle dysfunction, mitochondrial impairment, and increased chromosome segregation errors, leading to a progressive rise in embryonic aneuploidy. Consequently, the proportion of transferable euploid embryos declines substantially after age 35 and decreases even more rapidly after age 40. The introduction of preimplantation genetic testing for aneuploidy (PGT-A) has enabled comprehensive assessment of embryo chromosomal status before transfer.⁵ In addition to identifying euploid and aneuploid embryos, contemporary next-generation sequencing (NGS) platforms detect mosaicism and segmental chromosomal abnormalities with high analytical accuracy.^{2,4} Despite widespread clinical implementation of PGT-A, relatively few studies have analyzed large consecutive embryo cohorts from a single laboratory using standardized biopsy, vitrification, and genetic testing protocols.⁸ The present study evaluates chromosomal outcomes in 4,204 consecutive blastocysts and investigates the relationship between maternal age and embryo chromosomal competence.

Methods

Study Design

This retrospective cohort study was performed at the Georgian-German Reproductive Center (GGRC) in collaboration with IMC Genomix, Israel. All consecutive IVF/ICSI cycles undergoing PGT-A during the study period were reviewed. Institutional approval was obtained before analysis.

Patient Population

A total of 495 women fulfilled the inclusion criteria. Patients were categorized into three age groups:

Group	Age	Number of Patients
Group I:	20-29	90
Group II:	30-39	226
Group III:	40-43	179

Inclusion Criteria: IVF/ICSI treatment, PGT-A performed – Only patients with six or more biopsied blastocysts were included to ensure adequate embryo numbers for meaningful evaluation of chromosomal competence within each treatment cycle. This criterion minimized the influence of extremely poor responders while allowing robust embryo-level analysis.

Exclusion Criteria: Donor oocyte cycles, Structural chromosomal rearrangements, Monogenic PGT cycles, Incomplete genetic reports, and embryology procedures were excluded. Controlled ovarian stimulation was individualized according to ovarian reserve.

Following oocyte retrieval: Mature oocytes underwent ICSI. Embryos were cultured to the blastocyst stage. Trophectoderm Biopsy was performed on high-quality blastocysts. Embryos were vitrified immediately after biopsy. Samples underwent NGS-based comprehensive chromosome screening.

PGT-A Classification

Embryos were classified as:

Primary Outcome:	Secondary Outcome:
Euploid Embryo	Aneuploid Embryos
	Mosaic Embryos
	Segmental Abnormalities
	No-result

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation.
Categorical variables were summarized as percentages.
Comparisons among maternal age groups were performed using χ^2 tests for categorical variables and one-way ANOVA where appropriate.
Multivariable logistic regression may be used to assess the independent association between maternal age and embryo euploidy after adjustment for potential confounders. A p-value <0.05 was considered statistically significant.

Results

Overall Chromosomal Outcomes

A total of 4,204 blastocysts were successfully analyzed.
Overall, 2,826 embryos (67.2%) were classified as euploid, demonstrating a high proportion of chromosomally normal embryos within the study population. Aneuploid embryos represented 17.4% of all biopsied blastocysts, while mosaic embryos accounted for 5.7% and segmental abnormalities for 7.7%. Only 85 embryos (2.0%) yielded inconclusive results, reflecting excellent laboratory performance and high analytical reliability. The overall chromosomal distribution:

Chromosomal Status	%	Total Number
Euploid embryos:	67.2%	2826
Aneuploid embryos:	17.4%	731
Mosaic embryos:	5.7%	240
Segmental abnormalities:	7.7%	322
No-result rate:	2%	85

The laboratory demonstrated excellent technical performance, with only 2% of PGT-A results inconclusive.

Age-stratified analysis demonstrated a statistically significant decline in euploid embryo rates with increasing maternal age, accompanied by progressive increases in aneuploidy, mosaicism, and segmental chromosomal abnormalities. The laboratory maintained excellent analytical performance throughout the study period, with a technical failure rate of only 2%.

Maternal Age and Euploidy

A progressive decline in embryo euploidy was observed with advancing maternal age. Younger patients demonstrated the highest proportion of chromosomally normal embryos, whereas women aged 40-43 years exhibited the lowest euploid rates and the highest frequency of chromosomal abnormalities.

Group I (20-29 years)

This group demonstrated the highest embryo chromosomal competence, characterized by the greatest proportion of euploid embryos and the lowest incidence of aneuploidy.

Group II (30-39 years)

Women in this age group showed an intermediate decline in euploid embryo production together with modest increases in mosaic and segmental abnormalities.

Group III (40-43 years)

Advanced maternal age was associated with a marked reduction in euploid embryos and a substantial increase in chromosomal abnormalities, consistent with age-related meiotic dysfunction.

Discussion

The present study represents one of the largest single-center analyses of consecutive PGT-A blastocysts evaluating maternal age and embryo chromosomal competence.^{3,4,5}

The findings confirm that maternal age remains the strongest biological determinant of embryo ploidy.^{3,7,9} Although laboratory performance remained highly consistent throughout the study period, the proportion of chromosomally normal embryos decreased progressively with increasing maternal age.^{1,2,7}

This observation is biologically plausible and reflects age-dependent deterioration in oocyte quality, spindle integrity, mitochondrial function, and chromosome segregation during meiosis.^{5,7,9}

Importantly, the laboratory achieved an overall technical failure rate of only 2%, indicating excellent biopsy quality, DNA amplification, and sequencing performance. Such consistency strengthens the validity of the observed age-related differences.

These findings are consistent with previous reports from ESHRE, ASRM, and large multicenter PGT-A registries demonstrating increasing aneuploidy after age 35 years and an accelerated decline after age 40 years.^{9,13,14}

The present study further highlights the importance of individualized reproductive counseling and supports the clinical role of PGT-A in patients of advanced reproductive age.

Strengths: The principal strengths of this study include its large consecutive embryo cohort, standardized embryology laboratory procedures, use of a single validated NGS platform, inclusion

of consecutive clinical cases rather than selected populations, and excellent laboratory quality control, as reflected by the very low rate of inconclusive genetic results. These characteristics reduce methodological variability and strengthen the reliability of the observed associations.^{12,14}

Limitations

Its retrospective design and single-center setting limit the study. Additional multicenter prospective studies are needed to validate these findings. Clinical outcomes such as implantation, miscarriage, and live birth rates were not evaluated and should be investigated in future research.

Conclusions

In this large retrospective analysis of 4,204 consecutive blastocysts, maternal age was strongly associated with embryo chromosomal competence. Euploid embryo rates declined progressively with advancing age, while aneuploid, mosaic, and segmental abnormalities increased. Despite these biological differences, laboratory performance remained consistently high, with an exceptionally low rate of inconclusive PGT-A results.

These findings reinforce the central role of maternal age in reproductive prognosis and support the use of PGT-A as an important tool for individualized embryo selection and patient counseling, particularly in women of advanced reproductive age.

Future investigations should combine embryo chromosomal analysis with implantation rates, miscarriage rates, cumulative live birth rates, and neonatal outcomes.^{12,13} Additional multicenter prospective studies may further clarify the relationship between maternal age, embryo competence, and long-term reproductive success.

Declarations

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Conflict of Interest: The authors declare no competing interests.

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Research Article

THE IMPACT OF THYROID DYSFUNCTION ON THE DEVELOPMENT OF GESTATIONAL DIABETES MELLITUS AND PREGNANCY OUTCOMES: AN OBSERVATIONAL COHORT STUDY

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ABSTRACT

Background: Gestational Diabetes Mellitus(GDM) and thyroid dysfunction (TD) are the two most prevalent endocrinopathies during pregnancy.

Methods: The observational cross-sectional study was conducted in an outpatient clinic from May 2024 to May 2025. 72 patients with GDM (study group) and 40 volunteers (control group) were selected to participate in the study. Anthropometric data (body mass – BM, body mass index – BMI) and an oral glucose tolerance test were carried out for all participants during all three trimesters of pregnancy. Thyroid function (thyroid-stimulating hormone – TSH, thyroid antibodies) was assessed in the first trimester of pregnancy. A special structured questionnaire was developed for socio-economic and anamnesis data. Odds ratio (OR) and 95% Confidence intervals (95%CI) were assessed for factorial analysis.

Results: DM in the first trimester was manifested in 13 patients (18.1%), in the second trimester – in 42 patients (58.3%), in the third trimester – in 17 patients (23.6%). The presence of TD was a significant factor for GDM – the TD was revealed in 55 patients (76.4%) of the study group and 26 patients (54.2%) of the control group – OR = 2.74, 95%CI – 1.25-6.01, p=0.012. The percentage of patients with TSH more than 4 mcU/l was significantly higher in the study group compared to the control group (38.8% vs. 18.8%; OR=2.76, 95%CI – 1.16-6.56, p=0.022). It should also be noted that GDM in patients with TD was manifested significantly earlier than in patients without TD – 19.6±6.2 weeks vs. 24.8±4.4 weeks, t-test=3.21, p=0.002. Body mass gain at the end of the third trimester was also significantly higher in GD patients with TD compared to GDM patients without TD – 14.4±2.5 kg vs. 12.6±2.1 kg, t-test=2.69, p=0.009. The pregnancy in 30 patients (41.7%) with TD in the study group was achieved through IVF; IVF was used in 24 cases with TD (50.0%) in the control group. The difference was not significant. Therefore, the combination of IVF and TD cannot be considered a risk factor for GDM.

Conclusion: TD may be considered a noteworthy factor in the development of GDM. GDM may manifest earlier, and the patient’s body mass gain may be higher if TD is present during pregnancy. The combination of IVF and TD cannot be considered a risk factor for GDM.

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Keywords: gestational diabetes mellitus; in vitro fertilization; metabolic disorders; thyroid dysfunction; thyroid-stimulating hormone.

Introduction

Gestational Diabetes Mellitus (GDM) and thyroid dysfunction (TD) represent the two most common endocrine disorders complicating pregnancy. Both conditions are associated with significant short- and long-term maternal and fetal complications, including preeclampsia, cesarean delivery, macrosomia, and increased risk of future metabolic disease.¹⁻² Physiological changes during pregnancy profoundly influence both glucose metabolism and thyroid function. Thyroid hormones play a crucial role in regulating basal metabolic rate, insulin sensitivity, and pancreatic β -cell function. Even subtle alterations in thyroid function – particularly subclinical hypothyroidism and thyroid autoimmunity – have been linked to insulin resistance and impaired glucose tolerance.³⁻⁴ Recent studies suggest a growing interplay between thyroid function and glucose homeostasis during pregnancy. Thyroid dysfunction has been associated with an increased risk of gestational diabetes, possibly through mechanisms involving altered insulin signaling, chronic low-grade inflammation, and changes in adipokine regulation.^{5,6} Despite accumulating evidence, the strength and clinical relevance of the association between TD and GDM remain inconsistent across studies. Moreover, limited data exist regarding the influence of thyroid dysfunction on the timing of GDM onset and gestational weight gain – both of which are important determinants of pregnancy outcomes.⁷ Therefore, the aim of this study was to investigate the impact of thyroid dysfunction on the development of gestational diabetes, the timing of GDM onset, and selected clinical outcomes, including gestational weight gain.

Methods

Study Design and Population

This observational cohort cross-sectional study was conducted in an outpatient clinical setting between May 2024 and May 2025.

A total of 112 pregnant women were enrolled:

- 72 patients with gestational diabetes mellitus(study group)
- 40 healthy pregnant women (control group)

Inclusion criteria were:

- singleton pregnancy,
- age ≥ 18 years.

Exclusion criteria were:

- pre-existing diabetes,
- known thyroid disease under treatment,
- chronic systemic diseases.

Data Collection

Anthropometric measurements were obtained for all participants: body mass (BM), body mass index (BMI).

A structured questionnaire was used to collect:

- socio-demographic characteristics;
- medical and reproductive history (including IVF).

Laboratory Assessment

An Oral Glucose Tolerance Test (OGTT) was performed during all three trimesters:

- Thyroid function was assessed in the first trimester;
- Thyroid-stimulating hormone (TSH);
- Thyroid antibodies.

Definitions

Thyroid dysfunction (TD): defined based on elevated TSH (>4 mcU/L) and/or presence of thyroid antibodies.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD). The normality of data distribution was assessed using the Shapiro – Wilk test. For normally distributed variables, differences between groups were evaluated using the independent samples t-test or analysis of variance (ANOVA), as appropriate. Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated where applicable. Correlations between variables were assessed using the Pearson correlation coefficient (r). A p-value < 0.05 was considered statistically significant.

Results

Timing of Gestational Diabetes Diagnosis

GDM was diagnosed:

- First trimester: 13 patients (18.1%);
- Second trimester: 42 patients (58.3%);
- Third trimester: 17 patients (23.6%).

The Association between thyroid dysfunction and GDM shows that thyroid dysfunction was significantly more prevalent in the GDM group than in controls: 76.4% vs. 54.2%, respectively (OR = 2.74, 95% CI: 1.25-6.01, p = 0.012).

Table 1 shows the values of thyroid function parameters in the study GDM group and controls without GDM.

Table 1. Thyroid function parameters in the study GD group and controls.

Parameter	GDM group	Controls
	Mean ± SD	Mean ± SD
TSH, mcU/l	3.6 ± 2.5	2.7 ± 1.3
	t-test = 2.294, p = 0.024	
FT4, mcU/l	13.2 ± 2.0	13.4 ± 2.6
	t-test = 0.475, p = 0.636	
TG Dysfunction	GDM Group – n(%)	Controls – n(%)
Anti-Tg	22 (30.6%)	19 (39.6%)
	Chi2-test = 1.035, p = 0.309	
Anti-TPO	39 (54.2%)	28 (58.3%)
	Chi2-test = 0.201, p = 0.654	

Source:

Elevated TSH (>4 mcU/L) was also significantly associated with GDM: 38.8% in the GDM group vs. 18.8% in controls (OR = 2.76; 95% CI: 1.16-6.56, p = 0.022).

Impact on timing of GDM onset showed that GDM developed significantly earlier in patients with TD: 19.6 ± 6.2 weeks vs. 24.8 ± 4.4 weeks, respectively (t = 3.21, p = 0.002)

Patients with both GDM and TD had significantly higher weight gain: 14.4 ± 2.5 kg vs. 12.6 ± 2.1 kg (t = 2.69, p = 0.009).

IVF was used in:

- 41.7% of GDM patients with TD
- 50.0% of control patients with TD

No statistically significant difference was observed.

Discussion

This study demonstrates a significant association between thyroid dysfunction and the development of gestational diabetes. Women with TD had nearly a threefold increased risk of GDM, which is consistent with previous observational studies and meta-analyses reporting a positive association between elevated TSH levels and impaired glucose metabolism during pregnancy.^{5,8} One of the key findings of this study is that GDM occurred significantly earlier in women with TD. This observation suggests that thyroid dysfunction may accelerate the pathophysiological processes leading to insulin resistance. From a mechanistic perspective, hypothyroidism has been associated with reduced glucose uptake in peripheral tissues, increased hepatic glucose production, and dysregulation of lipid metabolism, all of which contribute to insulin resistance.^{3,9} Additionally, the greater gestational weight gain observed in women with TD may reflect underlying metabolic dysregulation. Thyroid hormones are known to influence energy expenditure and fat accumulation, and their deficiency may promote excessive weight gain during pregnancy. This is clinically relevant, as excessive gestational weight gain is independently associated with adverse maternal and neonatal outcomes.^{2,10} Interestingly, the combination of in vitro fertilization (IVF) and thyroid dysfunction was not associated with an increased risk of GDM in our study. This finding suggests that thyroid dysfunction itself may be a more critical determinant of metabolic disturbances than assisted

reproductive technologies. However, further studies with larger sample sizes are needed to confirm this observation.¹¹

From a clinical perspective, our findings support the importance of early screening for thyroid dysfunction in pregnancy. Identifying women with TD may allow for closer metabolic monitoring and timely implementation of preventive strategies aimed at reducing the risk of GDM and its complications.^{6,12}

Clinical Implications

- Early screening for thyroid dysfunction in pregnancy may help identify women at higher risk of GDM
- Closer metabolic monitoring may be warranted in patients with TD
- Preventive strategies could be implemented earlier in pregnancy

Limitations

Despite its high clinical importance, our study has several limitations. Among them are a relatively small sample size, a single-center design, a lack of stratification by type of thyroid dysfunction (subclinical vs. overt), and no adjustment for potential confounders (e.g., age, BMI, parity)

Conclusion

Thyroid dysfunction represents a significant risk factor for the development of gestational diabetes. It is associated with the earlier onset of GDM and increased gestational weight gain. These findings highlight the importance of early assessment of thyroid function during pregnancy and suggest a potential role for integrated endocrine screening strategies.

Declarations

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The authors declare no competing interests.

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Research Article

COMPARATIVE EFFECTS OF COMBINED INOSITOLS AND ALPHA-LIPOIC ACID (ALA) ON METABOLIC, HORMONAL, AND CLINICAL OUTCOMES IN OBESE HYPERINSULINEMIC WOMEN WITH POLYENDOCRINE METABOLIC OVARIAN SYNDROME (PCOS/PMOS): THE IMPACT OF FAMILY HISTORY OF DIABETES

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ABSTRACT

Background: Polyendocrine Metabolic Ovarian Syndrome (PCOS/PMOS) represents a complex metabolic-endocrine disorder in obese, hyperinsulinemic, and insulin-resistant women with a family history of diabetes. Myo-inositol (MI) and D-chiro-inositol (DCI) act as insulin-sensitizing agents, while alpha-lipoic acid (ALA) may provide additional metabolic benefits. However, comparative evidence regarding their combined effects in this high-risk population remains limited. Objective of the article is to compare the metabolic, hormonal, and clinical effects of MI, MI+DCI, and MI+DCI+ALA in obese, hyperinsulinemic women with PCOS/PMOS and a family history of diabetes.

Methods: In this randomized, double-blind, parallel-group clinical trial, 96 women aged 20–38 years with obesity (BMI ≥ 30 kg/m²), Rotterdam criteria-defined PCOS/PMOS, hyperinsulinemia, and insulin resistance were randomized to control, MI, MI+DCI (40:1), or MI+DCI+ALA groups. Participants were evaluated at baseline and after 12 and 24 weeks. Metabolic, hormonal, and clinical parameters, including insulin sensitivity, glucose metabolism, androgen status, lipid profile, anthropometric measures, and menstrual regularity, were assessed.

Results: After 24 weeks, all three treatment groups demonstrated improvements in metabolic and hormonal parameters compared with controls. The MI+DCI combination produced greater improvements in insulin resistance and glucose metabolism than MI alone, while the addition of ALA resulted in further improvement. Androgen levels decreased, and SHBG increased, accompanied by improved gonadotropin balance. Menstrual regularity was restored most frequently with MI+DCI+ALA, followed by MI+DCI and MI alone. Anthropometric and lipid parameters also improved, with the most pronounced overall metabolic effects observed with the triple combination. Improvements in hepatic insulin extraction and liver-related parameters were particularly evident following ALA addition.

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Conclusions: In obese women with PCOS/PMOS, hyperinsulinemia, insulin resistance and a family history of diabetes, MI+DCI supplementation was associated with greater metabolic, hormonal and clinical benefits than MI alone, while the addition of ALA provided further improvement across key metabolic outcomes. These findings support the potential role of combined inositol and ALA therapy in managing PCOS/PMOS phenotypes characterized by increased metabolic risk.

Keywords: alpha-lipoic acid; D-chiro-inositol; hyperinsulinemia; inositols; insulin resistance; metabolic risk; myo-inositol; PCOS; PMOS.

Introduction

Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS) is a significant public health issue with endocrine, reproductive, cardiometabolic, dermatologic, and psychological features. PCOS/PMOS is one of the most common conditions affecting around 10% of reproductive aged women, 1-5, with many remaining undiagnosed.^{1,2}

While its causal origins remain incompletely understood, accumulating evidence suggests metabolic dysfunctions – manifested by insulin resistance, obesity, hyperglycemia, and dyslipidemia – as key contributors to the pathogenesis and progression of PCOS/PMOS.³ Hyperinsulinemia and insulin resistance affect 50 to 80% of women with Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS), depending on different populations, ethnicities, and diagnostic methods. These metabolic abnormalities are more prevalent in overweight-obese women, even if exaggerated circulating insulin levels and reduced insulin-mediated glucose metabolism are also found in up to 40% of nonobese subjects.^{3,4}

Polyendocrine Metabolic Ovarian syndrome (PCOS/PMOS) is a complex metabolic-endocrine disorder in obese, hyperinsulinemic, and insulin-resistant (IR) women with a family history of diabetes.⁵

The inositol stereoisomers – Myo-inositol (MI) and D-chiro-inositol (DCI) act as insulin sensitizers.⁶ Inositols support the intracellular formation of insulin second messengers: phosphomyo-inositol-3-phosphate (PIP3) and inositolphosphoglycan (IPG).^{7,8}

The tissue-specific MI/DCI ratio depends on the activity of epimerase, the enzyme deputed to transform MI into DCI. Epimerase activity is stimulated by insulin and is reduced in the presence of insulin resistance. In the ovaries, which are insulin-sensitive, the physiologic MI/DCI ratio should be 100:1. In hyperinsulinemic women with PCOS/PMOS, the enzymatic epimerase activity is enhanced in the gonad, thus leading to a lower MI/DCI ratio at this level.⁸

The imbalance in the inositol pathway inside the ovary is believed to play a role in the ovulatory dysfunction of PCOS/PMOS. Therefore, during the past decades, oral nutritional supplementation with MI has been proposed as a novel therapy in these women. The treatment was reported to enhance insulin sensitivity and improve the clinical and hormonal characteristics of patients with PCOS/PMOS.^{7,8}

The Cochrane review found evidence that DCI may improve ovulation rate in the syndrome. There was no conclusive evidence that DCI affected BMI, WHR, or blood pressure, or hormonal parameters, except for serum SHBG levels, fasting glucose, fasting insulin, and lipids (total cholesterol and triglycerides). Given the lack of strong evidence, the new international guideline

offers cautious recommendations regarding the use of inositols: inositol (in any form) should currently be considered an experimental therapy for PCOS/PMOS, with emerging evidence of efficacy that highlights the need for further research.⁷⁻⁹

Recently, attention has also been focused on the role of Alpha-lipoic Acid (ALA), which shows additional benefits on glucose metabolism and oxidative balance. Alpha-lipoic acid (ALA), a biological antioxidant and a natural cofactor of mitochondrial dehydrogenase complexes, was originally investigated in patients with type 2 diabetes because of the close relationship between oxidative stress and insulin resistance.¹⁰

There is a growing body of evidence that ALA may act indirectly to maintain cellular antioxidant status by either inducing the uptake or enhancing the synthesis of endogenous low-molecular-weight antioxidants or antioxidant enzymes. Several studies have suggested that oral supplementation with ALA may improve insulin sensitivity in peripheral tissues and help maintain glycemic control in patients with diabetes mellitus.¹⁰ The hypothesized mechanism of action relies on stimulation of glucose uptake via intracellular redistribution of GLUT1 and GLUT4 transporters.¹¹

Oxidative stress is now recognized to play a central role in the pathophysiology of many different disorders;¹² among them is increased in women with Polyendocrine Metabolic Ovarian Syndrome, because of an increased production of free radicals associated with impaired plasma total antioxidant capacity (TAC) in both obese and normal-weight PCOS/PMOS women.¹³⁻¹⁵ The increased oxidant status could participate in the onset and maintenance of insulin resistance in these patients.¹⁶

However, evidence directly comparing the relative effectiveness of MI alone versus MI+DCI and MI+DCI+ALA combinations in these high-risk groups has remained limited.¹⁷⁻²¹

Our study aimed to evaluate the comparative effects of myo-inositol (MI) and D-chiro-inositol (DCI), combined with alpha-lipoic acid (ALA), on metabolic, hormonal, and clinical outcomes in obese women with Polyendocrine Metabolic Ovarian Syndrome (PCOS/PMOS), focusing on the impact of a family history of diabetes.

Methods

A randomized, double-blind, parallel-group clinical trial involving 96 obese patients (BMI $\geq$ 30 kg/m², age: 20- 38 years) with confirmed PCOS/PMOS according to the Rotterdam criteria, who had hyperinsulinemia and insulin resistance (IR) and a family history of diabetes (type 1 or type 2 diabetes). Subjects participating in the study, after informed consent, were randomly assigned to four main groups: (1) control (n=22), (2) MI 4 g/day (n=25), (3) MI + DCI (40:1 ratio; n=25), and (4) MI + DCI (40:1 ratio) + ALA 600 mg/day (n=24). Patients were assessed at baseline and at 12 and 24 weeks after the start of treatment.

Study participants underwent ultrasound scanning on days 3- 6 of menstrual bleeding. Target parameters for evaluation included the hormonal profile, OGTT, HOMA-IR, hepatic insulin extraction (HIE) index, lipid profile, BMI, hip circumference, and assessment of menstrual cycle regularity.

Results

After 24 weeks, all three study groups, in addition to the control group, showed significant metabolic and hormonal improvements. However, the MI+DCI group showed a significant decrease in HOMA-IR and 2-hour OGTT glucose levels, with further improvement in the MI+D-CI+ALA combination group.

Group:	HOMA – IR (Baseline)	HOMA-IR (12 weeks)	HOMA-IR (24 weeks)
Control	5.8	5.7	5.6
MI	5.9	4.9	4.5
MI+DCI	6.0	4.3	3.6
MI+DCI+ALA	6.1	3.9	2.9

Group:	2-hour OGTT glucose mg/dL – baseline	HOMA-IR (12 weeks)	HOMA-IR (24 weeks)
Control	168	166	165
MI	170	162	150
MI+DCI	172	150	135
MI+DCI+ALA	175	135	122

After 24 weeks, Hepatic insulin metabolism is significantly improved only in the triple combination. (MI+DCI+ALA) group.

Group:	HIE Baseline	HIE 12 weeks	HIE 24 weeks
Control	0.42	0.41	0.43
MI	0.41	0.45	0.48
MI+DCI	0.40	0.48	0.52
MI+DCI+ALA	0.40	0.52	0.60

In these groups, levels of common testosterone, androstenedione, and DHEAs decreased, while SHBG increased, leading to greater normalization of the LH/FSH ratio.

Parameters at Baseline and after 24 weeks:	Control	MI	MI+DCI	MI+DCI+ALA
TT (ng/dL)	78 → 76	80 → 65	82 → 54	84 → 48
Androstenedione (mg/mL)	3.9 → 3.8	4.0 → 3.2	4.1 → 2.7	4.2 → 2.3
DHEAs (µg/dL)	360 → 355	370 → 320	375 → 290	370 → 260
SHBG (nmol/L)	28 → 29	27 → 38	26 → 46	25 → 55

Group:	LH/FSH Ratio (Baseline)	LH/FSH Ratio (24 weeks)
Control	2.4	2.3
MI	2.5	1.9
MI+DCI	2.6	1.4
MI+DCI+ALA	2.7	1.2

The menstrual cycle was restored in 68% of the triple combination patients, in 64% of the inositols combination recipients, in 42% of the recipients of Myo-inositol, and in 18% of the control group.

Group:	The menstrual cycle restoration rate (%): 24 weeks
Control	18%
MI	42%
MI+DCI	64%
MI+DCI+ALA	68%

BMI, hip circumference, and lipid parameters improved with the same level of compliance in both the MI-only and MI+DCI combination groups, with no changes in liver enzymes or HIE; the latter parameters improved significantly in recipients of the triple combination. The dynamics of BMI and hip circumference also decreased accordingly.

Group:	BMI Baseline	BMI 12 weeks	BMI 24 weeks
Control	33.8	33.6	33.6
MI	33.9	33.1	32.9
MI+DCI	34.1	32.7	31.6
MI+DCI+ALA	34.2	31.9	30.3

Group:	hip circumference (cm) Baseline	hip circumference (cm) at 24 weeks
Control	112	111
MI	113	108
MI+DCI	114	105
MI+DCI+ALA	114	102

Key Findings

The combination of MI + DCI + ALA showed the strongest and most comprehensive effect in PCOS patients with obesity, insulin resistance, and familial diabetes risk, because it simultaneously improves Insulin sensitivity – Maximal reduction in HOMA-IR and 2-hour OGTT glucose; hepatic insulin metabolism – Significant improvement in hepatic insulin extraction (HIE); an-

drogen profile – Sharp decrease in androgens (TT, A4, DHEAS) and increase in SHBG; normalization of the LH/ FSH ratio; reduction in BMI and central adiposity; menstrual function - Highest frequency of menstrual cycle restoration.

Conclusions

Our study results support the evidence that the combined use of myo-inositol, D-chiro-inositol (40:1 ratio) and alpha-lipoic acid provides better metabolic, hormonal and clinical outcomes in obese PCOS/PMOS patients with hyperinsulinemia and insulin resistance (IR) and familial risk for diabetes, suggesting a preferential role for combination therapy in PCOS/PMOS phenotypes with high metabolic risk.

In the polyendocrine metabolic ovarian syndrome phenotype with high metabolic risk (family history of diabetes), the triple combination is the preferred therapeutic choice. However, further long-term and large-scale clinical studies are necessary to obtain more precise results, which will significantly improve therapeutic care strategies in high-risk PCOS/PMOS patients.

Declarations

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Review Article

APPLICATION OF MACHINE LEARNING PRINCIPLES IN THE MANAGEMENT OF HEMORRHAGIC SHOCK

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ABSTRACT

Background: Hemorrhagic shock remains one of the leading causes of preventable mortality in trauma, surgery, and obstetric emergencies. Early recognition, accurate prediction of clinical deterioration, and timely intervention are critical for improving patient outcomes. Advances in artificial intelligence (AI) and machine learning (ML), particularly gradient-boosted ensembles, recurrent neural architectures for physiological time series, and multimodal deep learning, have created new opportunities to support clinical decision-making by continuously analyzing high-dimensional physiological, laboratory, and imaging data streams. Objective: To review, from a technical and methodological standpoint, the machine learning architectures, feature engineering strategies, and validation frameworks applied to diagnosis, risk stratification, monitoring, and management of hemorrhagic shock, with emphasis on model design choices that affect clinical reliability.

Methods: A narrative review of contemporary literature was conducted, focusing on supervised, ensemble, and deep learning algorithms applied to trauma care, perioperative medicine, emergency medicine, and critical care. Studies evaluating predictive models based on electronic health records (EHR), continuous vital-sign telemetry, laboratory biomarkers, point-of-care ultrasound/imaging, and waveform-derived hemodynamic features were examined, with attention to model architecture, input feature space, validation methodology, and reported discrimination/calibration metrics.

Results: Ensemble tree methods (random forest, XGBoost, LightGBM) and recurrent/temporal architectures (LSTM, GRU, temporal convolutional networks, and transformer-based sequence models) applied to heart rate, blood pressure, lactate trajectory, hemoglobin/hematocrit trends, shock index and its derivatives, base excess, and photoplethysmography or arterial-waveform-derived features have demonstrated AUROC values frequently in the 0.80-0.93 range for predicting need for massive transfusion or hemorrhagic decompensation, generally outperforming threshold-based scores (e.g., ABC score, shock index alone) in retrospective

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cohorts. AI-assisted closed-loop and decision-support systems have been explored for titrating fluid resuscitation, blood product ratios, and vasopressor dosing, and for optimizing timing of surgical or endovascular hemorrhage control. Model interpretability (via SHAP, attention weights, or integrated gradients), external validation across heterogeneous populations, class imbalance in rare massive-hemorrhage events, and prospective clinical-workflow integration remain the principal technical barriers to deployment.

Conclusions: Machine learning represents a technically mature but clinically unproven adjunct to conventional assessment in hemorrhagic shock. Realizing its benefit requires rigorous external validation, post-deployment calibration monitoring, interpretable model outputs, and prospective multicenter trials demonstrating outcome benefit – not merely discrimination – before routine implementation in emergency and critical care workflows.

Keywords: machine learning; deep learning; artificial intelligence; hemorrhagic shock; clinical decision support; predictive analytics; trauma; critical care; massive transfusion; precision medicine; emergency medicine; time-series modeling; model interpretability.

Introduction

Hemorrhagic shock is a state of inadequate tissue perfusion resulting from acute blood volume loss, and it remains a leading cause of preventable death in trauma, postpartum hemorrhage, and major surgical or gastrointestinal bleeding. Conventional clinical assessment relies on discrete, often delayed indicators heart rate, systolic blood pressure, urine output, and serial hemoglobin measurements that may fail to capture the nonlinear, multivariate physiological trajectory preceding decompensation. Compensatory mechanisms (tachycardia, peripheral vasoconstriction) can mask significant volume loss until a critical threshold is crossed, at which point cardiovascular collapse can occur rapidly. Machine learning offers a fundamentally different paradigm: rather than applying static thresholds to individual variables, ML models can learn joint, time-varying, nonlinear relationships among dozens to hundreds of correlated physiological and laboratory features, continuously updating risk estimates as new data arrive. This review focuses specifically on the technical architecture of these systems the input feature space, model classes, training/validation methodology, and performance characterization rather than solely their clinical framing.¹⁻⁵ Pathophysiological Rationale for a Data-Driven Approach: Hemorrhagic shock progresses through compensated, decompensated, and irreversible phases, each characterized by distinct hemodynamic and metabolic signatures: rising shock index (heart rate / systolic BP), narrowing pulse pressure, rising lactate and falling base excess (reflecting anaerobic metabolism), falling central venous oxygen saturation, and coagulopathy (reflected in prolonged PT/INR, falling fibrinogen, and thromboelastography/thromboelastometry parameters such as clot amplitude and lysis index). Because these signals interact – e.g., lactate clearance kinetics are influenced by resuscitation volume, base deficit, and hepatic perfusion simultaneously – the underlying prediction problem is inherently multivariate and time-dependent, favoring ML approaches that model interaction effects and temporal dynamics over univariate threshold rules.⁶⁻⁹

Table 1. ML Architect and Hemorrhagic shock.

Model class	Typical use case	Technical notes
Logistic regression / regularized GLM (LASSO, ridge)	Baseline risk scores, interpretable comparators	Serves as the reference model against which more complex architectures are benchmarked; coefficients are directly interpretable.
Random forest / Extra Trees	Massive transfusion prediction, mortality risk	Robust to feature scaling and missingness; provides native feature-importance ranking (mean decrease in impurity)
Gradient boosting (XGBoost, LightGBM, CatBoost)	Structured EHR + lab data, tabular risk models	Frequently the top-performing tabular-data architecture; requires careful regularization and early stopping to avoid overfitting on rare-event outcomes
Recurrent networks (LSTM, GRU)	Continuous vital-sign streams, early-warning systems	Captures temporal dependencies in sequential vitals; sensitive to irregular sampling intervals, often requires imputation or time-aware embeddings
Temporal convolutional networks / transformers	ICU waveform and multivariate time-series forecasting	Attention mechanisms allow post-hoc interpretation of which time points drove a prediction; more data-hungry than RNNs
Convolutional neural networks	Point-of-care ultrasound (FAST exam) interpretation, imaging-based bleeding source localization	Applied to identify free fluid, active extravasation, or organ injury from ultrasound/CT
Reinforcement learning	Dynamic resuscitation policy optimization (fluid/vasopressor titration)	Largely investigational; raises significant safety and off-policy evaluation concerns before bedside deployment
Source: Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma. Sixth edition. Crit Care. 2023;27:80.		

Clinical Application Domains

Early detection and risk stratification

Models trained on rolling-window vital-sign and lab trends can flag patients trending toward decompensation before conventional early-warning scores (e.g., NEWS2, MEWS) trigger an alert, by learning nonlinear combinations of features rather than applying fixed point thresholds.

Massive transfusion and blood product requirement prediction

Supervised classifiers combining shock index, base deficit, hemoglobin, FAST exam findings, and injury mechanism have been used to predict need for massive transfusion protocol activation, aiming to reduce both under-triage (delayed blood product availability) and over-triage (unnecessary blood bank strain).

Resuscitation optimization

Decision-support models integrate dynamic preload-responsiveness indicators (pulse pressure variation, stroke volume variation) with lactate clearance trends to guide fluid versus blood product versus vasopressor sequencing, aiming to avoid both under-resuscitation and dilutional coagulopathy from excess crystalloid.¹²⁻¹⁶

Imaging-assisted diagnosis

CNN-based image analysis of point-of-care ultrasound and CT angiography has been applied to accelerate identification of active hemorrhage sites, supporting triage to surgical versus endovascular (angioembolization) intervention.

Model Validation and Performance Characterization

Rigorous evaluation of these models requires reporting beyond raw accuracy, given substantial class imbalance (massive hemorrhage events are comparatively rare): Discrimination: Area under the receiver operating characteristic curve (AUROC) and, given class imbalance, area under the precision-recall curve (AUPRC) are both necessary; AUROC alone can overstate performance on rare-event prediction tasks;

Calibration: Calibration plots and Brier score assess whether predicted probabilities match observed event rates – critical for a model informing transfusion or intervention thresholds; Temporal and external validation: Models should be validated on data from institutions, patient populations, and time periods distinct from training data; performance frequently degrades under external validation, reflecting dataset shift;

Interpretability tooling: SHAP (Shapley Additive Explanations) values, LIME, and attention-weight visualization are increasingly reported to allow clinicians to audit individual predictions rather than treat the model as a black box;

Decision-curve analysis: Net-benefit analysis across a range of clinically plausible decision thresholds is used to determine whether model-guided action would outperform treat-all or treat-none strategies in practice.

Technical and Implementation Challenges

Class imbalance and rare-event modeling: Massive hemorrhage and mortality outcomes are infrequent, requiring resampling strategies (SMOTE, class-weighted loss functions) or anomaly-

ly-detection framings that can introduce their own bias if not carefully validated. Missing and irregularly sampled data: Real-world ICU and trauma-bay data streams have variable sampling frequency and missingness patterns that are often informative (missing-not-at-random), requiring time-aware imputation or masking strategies rather than naive mean imputation. Generalizability and dataset shift: Models trained on a single trauma center's case mix, injury patterns, and resuscitation protocols may not transfer to different populations, resource settings, or blood-product availability contexts – a particularly relevant concern for adaptation in lower-resource health systems.

Interpretability versus performance trade-off: The highest-performing architectures (deep temporal models) are typically the least directly interpretable, creating tension with clinical accountability and regulatory requirements.

Prospective validation gap: The overwhelming majority of published models remain retrospective; few have undergone prospective, randomized evaluation demonstrating that model-guided intervention improves patient-centered outcomes rather than discrimination metrics alone. Regulatory and ethical considerations: Continuous learning systems that update model weights post-deployment raise validation and regulatory challenges (e.g., FDA's evolving framework for adaptive/continuously learning AI/ML-based software as a medical device); patient data privacy, consent for algorithmic decision support, and liability allocation for model-influenced clinical decisions remain unresolved.

Integration into clinical workflow: Alert fatigue from poorly calibrated early-warning systems can erode clinicians' trust; successful deployment requires careful threshold setting, human-in-the-loop design, and integration with existing EHR alerting infrastructure without disrupting workflow.

Future Directions

Promising directions include federated learning approaches that allow multi-institutional model training without centralizing sensitive patient data, thereby improving generalizability while addressing privacy constraints; multimodal fusion architectures that jointly model structured EHR data, waveform signals, and imaging; and reinforcement-learning-based closed-loop resuscitation systems evaluated first in silico and via retrospective off-policy evaluation before any bedside testing. Prospective, multicenter, ideally randomized trials comparing ML-guided decision support against standard-of-care management – powered on patient-centered outcomes (mortality, transfusion volume, organ dysfunction) rather than discrimination statistics alone – represent the necessary next step before these systems can be considered validated for routine clinical use.

Conclusion

From a technical standpoint, the machine learning toolkit applicable to hemorrhagic shock has matured substantially: ensemble tree methods and temporal deep learning architectures now consistently outperform static threshold-based scores in retrospective discrimination benchmarks, and interpretability tooling (SHAP, attention visualization) has narrowed – though not eliminated – the black-box concern. The translational gap lies not in model architecture but in external validation, calibration robustness under dataset shift, and, most critically, the near-absence of prospective outcome-based trials. Multicenter prospective validation and careful clinical-workflow integration remain prerequisites for moving these systems from promising retrospective analytics to trusted components of hemorrhagic shock management.

Declarations

Conflict of Interest: The authors declare no competing interests.

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Review Article

HIDDEN ERRORS IN IVF: FROM REPORTED INCIDENTS TO ELECTRONIC WITNESSING AND PROACTIVE RISK DETECTION

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ABSTRACT

Background: Errors involving gametes and embryos are uncommon but can have irreversible clinical, psychological, ethical, and legal consequences. Conventional incident reporting captures only events that are recognized and reported, whereas electronic witnessing systems (EWS) can also reveal mismatch conditions and near misses during routine laboratory work. To review the spectrum of reported IVF laboratory errors and non-conformances, summarize published data generated by IVF laboratories using electronic witnessing and structured risk-analysis systems, and examine how automation can shift safety practice from retrospective incident review toward prospective risk detection.

Methods: Narrative review of peer-reviewed studies, contemporary professional guidance, and regulatory data addressing IVF laboratory non-conformances, traceability, witnessing, mismatch events, and electronic witnessing. No unpublished or institution-specific data are included.

Results: In a 12-year Boston IVF series, 360 graded andrology/embryology non-conformances were identified across 36,654 cycles and at least 181,899 laboratory procedures; moderate and significant non-conformances together occurred in 0.23% of cycles and 0.045% of procedures, with no major events. A 10-year Brussels IVF EWS analysis included 109,655 cycles and 849,650 witnessing points: 2,132 mismatches (0.251% per witnessing point), including 144 critical mismatches, with a yearly mean critical mismatch rate of 0.017%. At Fertility North, 73,719 witnessing points from 11,210 cycles yielded 138 mismatches (0.19%) and 16 critical mismatches (0.02%); risk varied by time of day, procedure, and operator. FMEA studies show that structured traceability and EWS implementation can substantially reduce modeled mismatch risk. UK HFEA data for 2024/25 recorded 792 reported incidents across more than 100,000 cycles and 68 near misses, while more than 99% of cycles were completed without a reported incident.

Conclusion: Serious IVF identification errors are rare, but measurable upstream mismatch conditions persist even in mature laboratories. EWS should be viewed not merely as a substitute for manual double witnessing but as a real-time safety barrier, a source of near-miss intelligence and a component of a broader quality-management system.

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Keywords: IVF; electronic witnessing; near miss; specimen identification; traceability; patient safety; laboratory error; risk management; FMEA

Introduction

Assisted reproductive technology is unusually vulnerable to identification error because the biological materials being handled – oocytes, sperm, and embryos – cannot be reliably distinguished by visual inspection. At the same time, a contemporary IVF cycle requires repeated transfers between containers, workstations, and storage devices, often under substantial time pressure and cognitive load. A single failure of identification or traceability can therefore have consequences that are disproportionate to the apparent simplicity of the initiating deviation. The published safety literature shows an important paradox. Catastrophic events such as confirmed gamete or embryo mix-up are rare, yet minor deviations, near misses and mismatch conditions are measurable. Traditional incident-reporting systems predominantly describe events that have already been recognized. Electronic witnessing can expose an additional layer of risk by recording incompatible identifiers, workflow deviations and critical mismatch conditions at the time of handling.

This review examines IVF error through three complementary evidence streams: reported incidents and non-conformances; prospective risk analysis of vulnerable laboratory processes; and real-world data generated by electronic witnessing systems. The aim is not to estimate a universal IVF error rate; published denominators and definitions differ too substantially for that, but to identify reproducible safety patterns and the role of automation in preventing or intercepting error.

Methods

This article is a narrative review. Evidence was drawn from peer-reviewed studies of IVF laboratory non-conformances, traceability, FMEA and electronic witnessing; current professional guidance from ASRM/SRBT and ESHRE; and current regulatory incident data from the UK Human Fertilisation and Embryology Authority (HFEA). Priority was given to studies reporting explicit denominators such as cycles, procedures, witnessing points or mismatch events. Because terminology differs between publications, the original terms: non-conformance, mismatch, critical mismatch, protocol deviation and near miss, are retained where possible. No unpublished data from any institution are included in this version.

The Spectrum of Error in IVF

IVF safety events range from documentation and workflow deviations to loss or damage of gametes or embryos, cryostorage failures, incorrect genetic-test handling and, at the extreme, misidentification of reproductive material. ASRM/SRBT 2026 recommends grading protocol deviations from none/minimal through moderate, significant, and major, with major events including confirmed pregnancy or birth involving misidentified sperm, oocyte, or embryo and extreme events affecting multiple patients, such as storage-tank failure. The same guidance emphasizes that near misses are valuable safety signals rather than trivial events.

Legal data illustrate the disproportionate impact of laboratory errors. In a 10-year review covering 184,015 IVF cycles across practices insured by one malpractice carrier, 176 incidents led to 30 settled claims; 21 involved indemnity payments totaling 15.062 million US\$, and embryology errors accounted for eight settled claims.¹¹ A later US legal literature review identified 53

IVF malpractice cases from 1993-2022; 24 (45.3%) involved embryology errors, and 11 (20.8%) involved preimplantation genetic testing errors. Awards in that review ranged from 4,171 to 14.975 million US\$.¹²

What Conventional Non-conformance Reporting Reveals

The most detailed long-term single-laboratory analysis remains the Boston IVF series reported by Sakkas and colleagues. Between 2003 and 2015, 36,654 treatment cycles involved at least 181,899 laboratory procedures. After exclusion of quality-control statistical anomalies, 360 andrology/embryology non-conformance reports were graded: 277 none/minimal, 66 moderate and 17 significant; no major non-conformances were reported. Moderate and significant events combined occurred in 0.23% of cycles and 0.045% of procedures, approximately one per 441 cycles or one per 2,191 procedures.¹

The distribution of events is also informative. In the Boston IVF dataset, 52% of reported non-conformances occurred within embryology; cryopreservation accounted for 31% of moderate/significant non-conformances and PGT for 11%.¹ These findings demonstrate why a single global error rate is inadequate: risk is concentrated in specific processes, and the denominator chosen – cycle, procedure, or individual handling step – substantially changes the apparent frequency.

Regulatory Incident Data: The Visible Layer

National regulatory data provide a broader but differently defined view. The HFEA reported 792 incidents in UK-licensed clinics in 2024/25, 36% more than the 581 reported in 2023/24, across more than 100,000 treatment, storage, and donation cycles. More than 99% of cycles were completed without a reported incident. There were no Grade A incidents, 224 Grade B incidents, 443 Grade C incidents, and 68 reported near misses; 57 events were awaiting classification at the reporting cut-off. The HFEA explicitly cautions that the absence of reported incidents does not automatically indicate greater safety, as reporting patterns vary between clinics.

This distinction is central to IVF safety research. Incident databases measure detected and reported events; they do not directly measure all latent errors or interrupted error pathways. An increase in lower-grade reporting can therefore reflect a stronger safety culture rather than deterioration in care.

Why Manual Witnessing Is Not Enough

Manual double witnessing has long been used to protect chain of custody, but it is itself a human process. Repetitive checking can become automatic, require interrupting a second operator, and be vulnerable to distraction, confirmation bias, and ambiguous accountability. Electronic witnessing systems were developed to add an independent digital identification layer using barcode and/or radiofrequency identification (RFID), linking patient identity to laboratory consumables and requiring verification at predefined critical steps.

Current ASRM/SRBT guidance states that critical IVF procedures must be witnessed by a second person and/or a certified EWS, including oocyte and sperm preparation, insemination/ICSI, embryo movement, biopsy, cryopreservation, warming, transfer and disposal. The guidance also requires appropriate validation, training, documentation and investigation of electronic no-matches as near misses.⁶

Evidence From Electronic Witnessing Systems

Early electronic-witnessing observations

Early studies demonstrated that electronic witnessing could quantify mismatch conditions that conventional reporting rarely captured. A 2011 RI Witness conference abstract described 3,694 witnessing steps in 420 ART cycles. Sixteen mismatches were detected (0.43%); after excluding flow-chart/configuration and proximity-related events, four were attributed to human error, corresponding to 0.11% of witnessing steps.⁹ Because this evidence was published as a conference abstract rather than a full-length peer-reviewed article, it should be interpreted cautiously.

Ten years of electronic witnessing at Brussels IVF

The largest long-term published EWS dataset was reported by Sterckx and colleagues. Across 109,655 IVF/ICSI, frozen embryo transfer and IUI cycles, 724,096 RFID tags were used, and 849,650 witnessing points were registered. The system recorded 2,132 mismatch events, an overall rate of 0.251% per witnessing point and 1.944% per cycle. Of these, 144 were classified as critical mismatches. The yearly mean critical mismatch rate was $0.017 \pm 0.007\%$ per witnessing point and $0.129 \pm 0.052\%$ per cycle. In addition, 940 administrator-assigned events were recorded, including 320 critical administrator assignments.²

The study is particularly valuable because it separates total alerts from events judged critical, such as mislabelling or non-matching samples within one work area. Critical mismatches represented 144/2,132 (6.75%) of all mismatch events. Sperm preparation and IVF/ICSI were the procedures most prone to critical mismatch and administrator-assign events. The authors also cautioned that EWS can introduce new risks, including blind witnessing, if used incorrectly.²

Risk factors identified from 73,719 witnessing points

Forbrig and colleagues provided a complementary risk-factor analysis from Fertility North in Australia. Their retrospective dataset comprised 73,719 witnessing points from 11,210 consecutive treatment cycles between January 2016 and July 2023. They identified 138 mismatches (0.19%) and 16 critical mismatches involving biological material (0.02%); no actual mix-up occurred.³

Risk was not uniformly distributed. The overall mismatch rate was highest between 12:00 and 14:00 (0.28%), whereas the critical mismatch rate was highest after 16:00 (0.13%). Mismatch rates differed significantly across laboratory processes and operators. Embryo transfer had the highest overall mismatch rate (0.36%), while oocyte denudation had the highest critical mismatch rate (0.13%). Multivariable analysis associated oocyte denudation, embryo transfer, cryo-preservation, sperm preparation, oocyte collection, and insemination with mismatch risk; critical mismatch was, on univariate analysis, associated with work after 16:00 and oocyte denudation.³

Prospective Risk Analysis: FMEA and Traceability

Electronic witnessing is most effective when embedded within a broader process analysis. Rienzi and colleagues used failure mode and effects analysis (FMEA) to map seven IVF process phases, 19 process steps, and 32 possible failure modes. Before EWS implementation, the highest risk-priority number (RPN) was 30; after implementation, the highest RPN was 10.4. This does not demonstrate a two-thirds reduction in observed clinical errors; it demonstrates a reduction in the modeled risk score assigned to the highest-risk failure mode.

A subsequent multicentre Italian FMEA project developed a comprehensive IVF traceability protocol, reinforcing that identification safety requires a chain of controls rather than a sin-

gle witnessing step.⁵ Current ESHRE recommendations similarly place risk assessment, patient/sample identification and traceability, witnessing, validation, audits and management of non-conformities within the IVF laboratory quality-management framework.⁷

Comparing Published Electronic-Witnessing Data

Study	Setting / period	Exposure	All mismatches	Critical / true mismatches	Key observation
Thornhill et al. 2011 (conference abstract)	ART laboratory; short-term conference report	420 cycles; 3,694 witness steps	16 (0.43%)	4 human-error true mismatches (0.11%)	Early demonstration that EWS detects and classifies mismatch conditions
Sterckx et al. 2023	Brussels IVF; 2011–2021	109,655 cycles; 849,650 witnessing points	2,132 (0.251%/WP)	144; yearly mean 0.017%/WP	Large long-term dataset; only a minority of alerts were critical
Forbrig et al. 2025	Fertility North; 2016–2023	11,210 cycles; 73,719 witnessing points	138 (0.19%)	16 (0.02%)	Risk varied by time, process and operator; no actual mix-up

Direct numerical comparison between studies should be approached with caution. Electronic platforms differ in workflow architecture and alert logic, while authors use different definitions of mismatch, true mismatch, critical mismatch and administrator intervention. Nevertheless, the studies consistently show that measurable mismatch conditions persist during routine ART work and that only a subset of total alerts represents a biologically critical event.

From Error Prevention to Risk Intelligence

The most important contribution of EWS may be conceptual. A conventional witness answers a binary question at a critical moment: do these identifiers match? A mature electronic system can also create a longitudinal dataset describing where and when alerts occur, which workflow steps generate technical noise, and whether corrective actions change recurrence. This turns witnessing from a compliance task into a potential source of safety intelligence. Such data should not be used primarily to rank or blame individual embryologists. Operator-level variation may identify training or workflow needs, but errors in complex systems usually arise from interactions among workload, process design, interruptions, staffing, equipment, software, and human behavior. ASRM/SRBT therefore recommends nonpunitive reporting, continuous surveillance, root cause analysis, and corrective action. A just culture is especially important because under-reporting destroys the very data needed for prevention.

Cryostorage: Extending the Chain of Identity

The next logical boundary for electronic witnessing is long-term cryostorage. As cryobanks expand, safety depends not only on confirming specimen identity at freezing and warming but also on maintaining reliable linkage among patient identity, the individual cryogenic container, and its physical storage location throughout the storage lifecycle.

An integrated cryostorage-management model could make each movement into, within, or out of storage a controlled, traceable event, reducing dependence on manually maintained location records and strengthening protection against misplacement or retrieval of an incorrect specimen. Commercial approaches such as CryoControl and location-identification tools such as Cryo-Spacer illustrate this direction, but their clinical impact should be evaluated independently rather than inferred from product functionality alone. The broader principle is a continuous chain of custody: identity, location, and action should remain traceable from specimen creation to final disposition.

Patient acceptability is also relevant. In a prospective single-centre cohort of 408 patients, 90.4% expressed significant concern about sample mix-up; use of an EWS reduced those concerns in 92.1%, and 97.1% reported high satisfaction with electronic traceability.¹⁰ These findings address patient perception rather than laboratory error prevention, but they illustrate the importance patients place on visible traceability safeguards.

Beyond mismatch prevention, EWS can reduce the operational burden of manual double witnessing. A prospective timing study found substantial reductions in witnessing time across ICSI, Day-3 embryo assessment, fresh embryo transfer and frozen embryo transfer.¹³

Limitations of the Evidence

The literature has important limitations. There is no universal taxonomy of IVF laboratory errors, and denominators vary across cycles, procedures, tags, and witnessing points. Reporting systems are influenced by local safety culture, regulatory requirements, and willingness to report. EWS platforms differ in hardware, software logic, and workflow configuration, and a mismatch alert does not prove that an adverse event would have occurred without intervention. Much of the evidence is retrospective and single-center. Finally, some early EWS data were published only as conference abstracts. These limitations preclude a single pooled 'IVF error rate' and argue for standardized definitions and multicentre reporting.

Practical Implications for IVF Laboratories

Available evidence supports a layered safety model. Laboratories should maintain unambiguous labeling and chain-of-custody procedures; witness critical specimen movements; validate and audit EWS where used; classify and investigate no-matches and protocol deviations; monitor mismatch and technical-alert trends; and use root-cause analysis and prospective risk tools such as FMEA. 4-7 Electronic witnessing may also improve workflow efficiency: in a prospective comparison of 342 witnessing observations, EWS reduced total witnessing time by approximately 3.1 – to 5.2-fold across four common IVF procedures.¹³ The objective is not zero reporting. A laboratory that detects, reports, and learns from near misses may be safer than one that reports none.

Conclusion

IVF laboratory errors are rare at the level of catastrophic outcome but are not absent at the level of process deviation and near miss. Conventional non-conformance reporting, regulatory

surveillance, and electronic witnessing describe different layers of the same safety problem. Published EWS datasets involving hundreds of thousands of witnessing points show that mismatch conditions can be detected during routine work, that biologically critical mismatches form only a minority of total alerts, and that risk clusters around particular processes and working conditions. Electronic witnessing should therefore be understood as more than an automated second witness. When implemented correctly within a quality-management system, it can provide real-time interception, traceability, and a measurable dataset for proactive risk reduction. The future direction is a continuous digital chain of identity and location extending from gamete collection through embryo culture, genetic testing, cryostorage, warming, transfer, and final disposition.

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Declarations

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Table 1. Selected published evidence relevant to IVF laboratory error and electronic witnessing

Evidence source	Population / denominator	Main findings	Interpretation
Boston IVF non-conformance database	36,654 cycles; ≥181,899 procedures	277 minimal, 66 moderate, 17 significant, 0 major; moderate+significant 0.045%/procedure	Structured reporting reveals low-frequency but recurrent process failures
Brussels IVF EWS	109,655 cycles; 849,650 witnessing points	2,132 mismatches (0.251%/WP); 144 critical; mean critical rate 0.017%/WP	Long-term EWS detects a measurable hidden layer; most alerts are not critical
Fertility North EWS	11,210 cycles; 73,719 witnessing points	138 mismatches (0.19%); 16 critical (0.02%); no mix-up	Mismatch risk varies by time, process and operator
Rienzi FMEA	7 phases; 19 steps; 32 failure modes	Highest RPN decreased from 30 to 10 after EWS	EWS plus process redesign reduced modeled mismatch risk
HFEA 2024/25	>100,000 UK cycles	792 reported incidents; 68 near misses; >99% of cycles without a reported incident	Regulatory reporting captures visible events but is sensitive to reporting culture

Review Article

VISCOELASTIC AND RHEOLOGICAL PROPERTIES OF SEMEN AND THEIR ROLE IN FERTILIZATION

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ABSTRACT

Semen is a complex biological fluid characterized by specific physicochemical properties. Among these, viscoelastic and rheological properties play a particularly important role, directly influencing sperm motility, transport through the female reproductive tract, and successful fertilization. The study of these properties is of great importance for both fundamental reproductive biology and clinical andrology and reproductive medicine.

Keywords: rheology properties, semen, viscoelasticity.

Introduction

Rheology is a cross-disciplinary field that studies the flow and deformation of matter. At the beginning of the last century, rheology was mainly related to physics and analytical chemistry; however, today rheological research has become an important area of both fundamental and applied biomedicine. All biological fluids, including semen, are non-Newtonian. Their viscosity varies with the deformation rate and external conditions. The main rheological characteristics of semen include: viscosity, elasticity, fluidity, liquefaction time, thixotropy, and shear resistance.

Materials and Methods

We analyzed contemporary literature available in PubMed using filters for the years 2022-2026 and the keywords “viscoelastic properties of human semen” and “rheological properties of human semen”. The keywords included both phrases and individual terms. Based on the analysis of the selected articles, the main concepts were systematized and integrated into the fundamental framework of the presented results.

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Results

Semen Viscosity

Viscosity is the ability of a fluid to resist flow. Normal semen after ejaculation has a relatively thick consistency; however, within 15-60 minutes it undergoes liquefaction under the action of prostatic enzymes. Increased semen viscosity is referred to as hyperviscosity and may lead to decreased sperm motility, impaired penetration through cervical mucus, and reduced probability of natural fertilization.¹

Elasticity

Elasticity characterizes the ability of semen to restore its shape after mechanical stress. It is determined by interactions between seminal plasma proteins, mucins, and other macromolecules. Excessive elasticity may hinder free sperm movement, whereas moderate viscoelastic properties help retain the ejaculate within the female reproductive tract.²

Composition of Semen and Formation of Its Rheological Properties

Semen consists of: spermatozoa; seminal vesicle secretions; prostatic secretions; seminal plasma proteins; semen lipids; semen enzymes; ions and water. Seminal plasma proteins form the structural basis of semen and participate in the regulation of sperm function. These mainly include: structural proteins responsible for temporary semen coagulation after ejaculation; transport proteins that bind and transport ions, hormones, lipids, and trace elements; enzymatic proteins involved in catalytic functions and in semen liquefaction; and immune proteins that protect spermatozoa from immune reactions and microorganisms. Important seminal proteins include: semenogelins, albumins, globulins, fibronectin, and lactoferrin. Lipids are components of sperm membranes and seminal plasma. They are essential for maintaining cellular structure and energy metabolism. Major semen lipids include: phospholipids, which form sperm membranes; cholesterol, which regulates membrane fluidity and participates in capacitation; fatty acids, serving as energy sources and membrane components; and sphingolipids involved in cell signaling. Semen enzymes play an important role in sperm viability, semen liquefaction, and fertilization. Most enzymes originate from the prostate gland and seminal vesicles. The major enzymes include: prostate-specific antigen (PSA), responsible for semen liquefaction after ejaculation through degradation of coagulum proteins; hyaluronidase, which helps sperm penetrate the oocyte coverings by degrading hyaluronic acid; acrosin, a proteolytic enzyme involved in zona pellucida penetration; and acid phosphatase, a marker of prostatic secretion.^{3,4}

Table 1. Main Factors Affecting Semen Rheology.

Factor	Influence
Seminal plasma proteins	Form gel-like structures
Fibrinogen-like substances	Provide coagulation after ejaculation.
Prostatic enzymes	Cause semen liquefaction
Environmental pH	Alters motility and viscosity
Cell concentration	Influences flow resistance

Mechanism of Changes in Semen Viscosity After Ejaculation

After ejaculation, semen undergoes two sequential stages: coagulation and liquefaction. Immediately after ejaculation, semen becomes thicker. This contributes to: retention of semen in the vagina; protection of spermatozoa from the acidic environment; reduction of seminal fluid loss. Proteins secreted by the seminal vesicles mediate coagulation. Within 15-60 minutes, under the influence of prostate-specific antigen (PSA), protein structures are degraded, and semen becomes more fluid. Liquefaction is necessary for: activation of sperm motility; penetration through cervical mucus; migration toward the oocyte.^{3,5}

Role of Rheological Properties in Fertilization

The role of rheological properties in fertilization is extensive, although modern scientific literature contains relatively few studies specifically focused on semen rheology. Semen rheology influences sperm motility. Spermatozoa move within a complex viscoelastic environment, and their flagella must overcome fluid resistance. Optimal viscosity ensures effective sperm progression, reduced energy expenditure, and protection from mechanical damage. Excessive viscosity decreases sperm velocity and reduces the likelihood of reaching the oocyte.^{2,3,6}

Penetration Through Cervical Mucus

Cervical mucus itself possesses pronounced rheological properties. Successful sperm penetration requires appropriate compatibility between semen viscosity, cervical mucus structure, and flagellar activity. Disruption of these interactions may reduce the probability of fertilization. Modern studies demonstrate that in viscous environments spermatozoa can generate collective movements and microflows that enhance migration efficiency. Such hydrodynamic interactions are especially important within the fallopian tubes.^{5,6}

Pathological Changes

On one hand, Semen hyperviscosity, considered a pathological marker, may develop due to: inflammatory diseases; genital tract infections; oxidative stress; impaired prostate function; increased leukocyte concentration. On the other hand, impaired liquefaction associated with insufficient activity of prostatic enzymes results in persistently thick semen. This condition may be caused by: chronic prostatitis, hormonal disorders, zinc deficiency, and prostate diseases.⁶

Methods for Studying Semen Rheology

The investigation of semen rheology combines laboratory and high-technology methods, including viscometry, rheometry, microscopy, liquefaction time analysis, and computer-assisted sperm analysis (CASA). These investigations help diagnose male infertility, assess treatment efficacy, select assisted reproductive technologies (IVF, ICSI), and predict the probability of natural conception.⁷

Conclusion

Viscoelastic and rheological properties of semen play a crucial role in the reproductive process. They determine the efficiency of sperm transport, the ability of spermatozoa to overcome barriers within the female reproductive tract, and ultimately to reach and fertilize the oocyte. Alterations in these properties may significantly reduce male fertility and represent one of the causes of infertility. Modern diagnostic methods allow detailed investigation of

semen rheological characteristics and enable the use of these findings to optimize treatment and assisted reproductive technologies. The study of semen as a complex biophysical system remains an important and promising area of modern medicine and biophysics.

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Review Article

SURGICAL MANAGEMENT OF BREAST CANCER DIAGNOSED DURING PREGNANCY: A NARRATIVE REVIEW

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ABSTRACT

Background: Breast cancer diagnosed during pregnancy (PrBC) represents a rare but increasingly prevalent clinical scenario, driven by delayed childbearing and increasing breast cancer incidence among premenopausal women. PrBC is characterized by distinct biological features – including a predominance of hormone receptor-negative, poorly differentiated, and lymph node-positive tumors – and poses unique therapeutic constraints. Surgery constitutes the cornerstone of locoregional management; however, evidence-based guidance remains limited to observational data and expert consensus, because randomized controlled trials are ethically precluded in this population.

Methods: A narrative review of the current literature was conducted, incorporating prospective cohort studies, systematic reviews, meta-analyses, and major international guidelines – including the 2023 ESMO Expert Consensus Statements, the 2025 ASCO Sentinel Lymph Node Biopsy Guideline Update, the 2025 RCOG Green-top Guideline No. 12 on Pregnancy and Breast Cancer, and the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer (Version 2.2026) – to synthesize evidence on all aspects of surgical care for breast cancer diagnosed during gestation.

Results: Surgery can be performed safely at any stage of pregnancy. The optimal procedure – breast-conserving surgery (BCS) or mastectomy – is determined by tumor biology, gestational age, and the feasibility of adjuvant radiotherapy, which must be deferred until the postpartum period. Sentinel lymph node biopsy (SLNB) using technetium-99m is considered safe and endorsed by most current guidelines as the standard axillary staging approach in clinically node-negative PrBC, while blue dye agents such as isosulfan blue and methylene blue are discouraged. Venous thromboembolism (VTE) prophylaxis with low-molecular-weight heparin represents a critical yet historically underemphasized component of perioperative care, given the compounded thrombotic risk conferred by pregnancy, malignancy, and surgery.

Conclusion: Definitive surgical treatment of PrBC, delivered within a dedicated multidisciplinary framework, can achieve locoregional control comparable to that in non-pregnant patients.

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Therapeutic conservatism at the expense of oncological adequacy must be avoided. Prospective registry data and validation of novel axillary staging approaches – including targeted axillary dissection – in the PrBC setting remain important research priorities.

Keywords: breast cancer; breast-conserving surgery; mastectomy; pregnancy; PrBC; sentinel lymph node biopsy; targeted axillary dissection; venous thromboembolism.

Introduction

Breast cancer is the most frequently diagnosed invasive malignancy during pregnancy.¹ Breast cancer during pregnancy (PrBC) and postpartum breast cancer were grouped under the umbrella term “pregnancy-associated breast cancer” (PABC). Breast cancer diagnosed during pregnancy (PrBC) is defined as invasive or in-situ breast cancer identified at any gestational age, from conception to delivery. This definition intentionally excludes malignancies diagnosed in the postpartum or lactational periods, which, despite sharing epidemiological and clinical features with PrBC, carry distinct biological microenvironments, metastatic propensities, and therapeutic windows. The clinical and biological differentiation between PrBC and postpartum breast cancer has gained increasing recognition in the literature.^{2,3}

The diagnosis and management of PrBC present significant challenges, including delayed recognition, the complexity of therapeutic decisions, ethically sensitive issues such as potential pregnancy termination, and the concurrent care of both mother and fetus. The interval between symptom onset and diagnosis is typically longer compared with non-pregnant controls, suggesting diagnostic delay.^{4,5} diagnosis, prognosis, and effective treatment modalities of pregnancy-associated breast cancer (PABC). Furthermore, physiological changes of the breast during pregnancy reduce the effectiveness of imaging modalities.⁶ The ultimate goal is to provide oncologic management comparable to that of non-PABC breast cancer while ensuring maternal and fetal safety. Moreover, optimal management requires a multidisciplinary approach involving general surgery, medical oncology, obstetrics, radiation oncology, genetics, nursing, and psychosocial support.

The 2023 ESMO Expert Consensus Statements on PrBC management represent a key reference.⁷ Crucially, 2025 has seen two landmark guideline publications that substantially advance the formal endorsement of surgical approaches previously supported only by observational evidence: the updated ASCO Sentinel Lymph Node Biopsy Guideline, which includes pregnant patients as a recognized special circumstance and states that clinicians may offer SLNB in this population using technetium-99m;⁸ and the Royal College of Obstetricians and Gynecologists (RCOG) Green-top Guideline No.12 on Pregnancy and Breast Cancer, which designates Tc-99m-guided SLNB as the standard of care in clinically node-negative PrBC and recommends LMWH thromboprophylaxis given the risk conferred by pregnancy, cancer, and surgery.⁹ We aimed to synthesize the available surgical evidence, incorporating all current guidelines, with attention to TAD, axillary surgery de-escalation, and VTE prophylaxis.

Epidemiology, Risk Factors, and Genetic

The reported incidence of PrBC ranges from 3 to 7.7 per 100,000 deliveries, and this figure is projected to rise as delayed childbearing becomes more prevalent.^{10,11} Among women younger than 45 years, PABC accounts for 2.6-6.9% of breast cancer cases.¹²

A 2025 national claims-based analysis of 1,189 PABC patients in the United States reported that the proportion of breast cancer cases meeting the traditional PABC definition rose sig-

nificantly from 2.36% (2007-2009) to 3.94% (2019-2021; $p < 0.001$). It must be noted that this dataset does not stratify intrapartum from postpartum cases, and therefore does not provide PrBC-specific incidence trends.¹³

Risk factors for PrBC are similar to those for breast cancer in general, including early menarche, late menopause, nulliparity, dietary factors, sedentary lifestyle, ethnicity, and family history.⁶ The increasing incidence of PrBC is largely attributable to the trend of delayed childbearing into older ages, where breast cancer risk is inherently higher, combined with the overall rising incidence of breast cancer in premenopausal women.⁷

Hormonal surges during pregnancy (particularly estrogen, progesterone, and insulin-like growth factor-1) have been implicated in promoting tumor cell proliferation. Immunological tolerance mechanisms required for fetal survival share overlapping checkpoint pathways with tumor immune evasion, including progesterone-stimulated expression of shared onco-fetal immune checkpoints such as B7-H4.¹⁴⁻¹⁶

Genetic testing is recommended for patients diagnosed with breast cancer under the age of 40. Since PrBC often occurs in this age group, genetic testing should also be considered.¹⁷ While the optimal timing of testing remains debated, performing it prenatally may aid treatment and prenatal genetic counseling. Most susceptibility genes are inherited in an autosomal dominant pattern, giving a 50% risk of transmission to offspring. Parents may request testing to determine their children's carrier status.¹⁸ Although the association between BRCA1/2 mutations and PABC has not been fully established, these mutations are more frequent in younger patients and have been reported more commonly in PABC cohorts. Several studies also report a higher prevalence of family history in PABC compared with controls.^{5,19}

Tamoxifen used for risk reduction is contraindicated during pregnancy and in women planning pregnancy in the near future.²⁰

Presentation

The most frequent presenting symptom of PABC is a painless palpable mass. Other common findings include skin thickening, asymmetric breast enlargement, and nipple discharge, which can be mistaken for physiological changes of pregnancy. Accessory breast tissue may also enlarge during pregnancy and mimic a tumor.²¹ Although the clinical presentation of breast cancer in pregnant and non-pregnant patients is broadly similar, any suspicious mass persisting for more than one week, unexplained nipple discharge, or erythema warrants further evaluation. Nonetheless, approximately 80% of palpable breast masses during pregnancy are benign.^{9,22,23} The interval between symptom onset and diagnosis is longer in PrBC compared with non-pregnancy-related breast cancer, and is significantly associated with overall survival.^{4,24}

Pathological Features

Invasive ductal carcinoma accounts for 78-88% of PrBC cases.²⁵ NCCN guidelines specify that PrBC tumors are more frequently poorly differentiated, more often ER/PR negative, and approximately 30% are HER2 positive.²⁶ The largest study included 311 pregnant and 865 non-pregnant patients, in which the proportion of ER-negative tumors was almost doubled in pregnant compared to non-pregnant patients (53.4% versus 25.5%). Tumors diagnosed during pregnancy were shown to have a high level of receptor activator of nuclear factor-kappa B ligand (RANKL).^{27,28}

Diagnosis and Staging

Accurate preoperative staging directly determines the choice of operative procedure. Breast ultrasound (US) is the first-line imaging modality, achieving sensitivity and specificity of 80.1% and 88.4%, respectively, without ionizing radiation exposure.²⁹ Mammography is indicated when clinical or sonographic findings raise concern for malignancy; the resulting fetal radiation dose of <3 mGy is well below the threshold of concern. Contrary to prior practice, the American College of Radiology now advises against fetal shielding during mammography, as shielding produces scatter radiation and paradoxically increases rather than reduces fetal dose; without a shield, fetal exposure is negligible, whereas NCCN v2.2026 continues to recommend mammography with shielding.^{26,30,31}

Non-contrast breast MRI incorporating diffusion-weighted imaging (DWI) sequences is recommended in selected cases by ESMO 2023, with sensitivities of 72.4-97% for nodal staging and the ability to detect multifocality and contralateral involvement not apparent on US, without the fetal risks associated with gadolinium contrast, which is contraindicated in pregnancy.^{7,29} Gadolinium agents are associated with stillbirth, neonatal death, and inflammatory skin disorders and must be avoided.³²

Cumulative fetal radiation exposure exceeding 100 mGy must be avoided as it increases the risk of fetal death, growth restriction, microcephaly, and intellectual disability. Current imaging techniques generally remain below the 50 mGy threshold, which is not associated with increased anomalies or pregnancy loss. However, it is important to mention stochastic effects, which even low-dose exposure carries potential long-term risks of fetal carcinogenesis or genetic damage. Therefore, ionizing radiation should be used only when strictly indicated, at the lowest possible dose.³³

Ultrasound-guided core needle biopsy is the preferred method for histological diagnosis in pregnancy due to the absence of ionizing radiation and ease of use. Stereotactic biopsy and MMG-guided wire localization can also be safely performed when ultrasound is insufficient. Core biopsy carries a slightly increased risk of bleeding and infection in pregnancy.^{34,35}

For axillary staging, ESMO 2023 specifically highlights the role of US-guided core biopsy or fine-needle aspiration cytology (FNAC) of morphologically suspicious lymph nodes. With a specificity of 95.7-100% and a high positive predictive value, a positive FNAC result justifies proceeding directly to primary ALND or, in patients receiving NACT, planning TAD rather than SLNB, thereby avoiding two separate axillary procedures.⁷

For staging clinically node-negative T1-T2 tumors, abdominal ultrasound and chest X-ray with abdominal shielding, liver function and renal function assessment, and a CBC are preferred in pregnancy.^{26,36} Non-contrast spinal MRI may be used to detect bone metastases.³⁷ CT scans and PET/CT are generally avoided due to fetal radiation exposure.³⁸

Pregnant women with breast cancer require close monitoring with serial ultrasounds and routine prenatal examinations. Continuous fetal assessment is essential and should be overseen by an obstetrician. If developmental anomalies are suspected, more advanced diagnostic evaluations, including amniocentesis, may be warranted.³⁶

Surgical Management

Physiological changes during pregnancy- such as rapid PaO₂ decline during brief apnea, progesterone- and prostaglandin-induced mucosal changes, and altered hemodynamics can contribute to intubation challenges. Intraoperatively, it is essential to maintain maternal blood

pressure within normal limits and avoid maternal hypoxemia or hypercapnia. Anesthetic agents currently in use have not been associated with teratogenicity when administered for durations of less than three hours.³⁹

The modified radical mastectomy has been the most common procedure in PrBC.²⁶ Surgical options for breast cancer in pregnancy include breast-conserving surgery (BCS), mastectomy, and oncoplastic techniques. The choice of procedure depends on multiple factors such as tumor stage, size, and gestational age. The 2025 Seminars in Perinatology practical guidelines confirm that surgery can be performed in any trimester, identifying the second trimester (12-24 weeks) as the optimal window owing to the completion of organogenesis, the lowest risk of spontaneous abortion, and the absence of late-gestational hemodynamic constraints.^{6,40} Table 1 summarizes surgical approaches by trimester.

In the first trimester, termination of pregnancy should be discussed with the patient. The patient should be informed that termination of pregnancy has not been shown to improve prognosis; however, the decision belongs to the patient, and her choice should be supported without reservation.^{9,26} Mastectomy has traditionally been preferred in the first trimester because adjuvant radiotherapy cannot be initiated during pregnancy without unacceptable fetal exposure, and the interval to delivery is too prolonged to permit safe RT deferral. However, NCCN v2.2026 explicitly states that BCS during the first trimester can be considered in patients who will require adjuvant chemotherapy and can have adjuvant RT delayed until after delivery – a meaningful shift from the prior dogma of routine mastectomy in the first trimester. Immediate reconstruction following mastectomy may be deferred until delivery to limit operation duration.^{26,36}

The second trimester offers the most favorable conditions for breast surgery. Both BCS and mastectomy are viable options, and the decision follows the same oncological principles as in non-pregnant patients. Current evidence supports delaying radiotherapy until after delivery without compromise of locoregional control in carefully selected patients.^{9,26}

In the third trimester, BCS is particularly well-suited, as adjuvant radiotherapy can begin in the early postpartum period without a clinically significant delay. For patients earlier in the third trimester with larger or more complex tumors, mastectomy remains an appropriate choice.²⁶ Chemotherapy administered within three weeks of delivery significantly increases the risk of maternal-neonatal myelosuppression. Chemotherapy should be completed at least three weeks before the anticipated delivery date.^{26,41}

Axillary staging in PrBC is indispensable for prognostic stratification, planning systemic therapy, and determining the need for regional radiotherapy. In a landmark development, the 2025 ASCO Sentinel Lymph Node Biopsy Guideline Update formally includes pregnant patients as a recognized special circumstance for the first time, explicitly recommending that SLNB can be offered to pregnant patients with clinically node-negative breast cancer.^{8,42} However, an important discrepancy in guidelines must be acknowledged: the NCCN guideline takes a substantially more cautious position, stating that there are insufficient data to support recommendations for SLNB in pregnant patients and that decisions should be individualized. Furthermore, NCCN cites a review concluding that SLNB should not be offered to pregnant patients before 30 weeks of gestation.²⁶

The use of technetium 99m (Tc99m) is considered safe. The ASBrC Oncolactation Resource Guide (2024) recommends same-day administration of the radiotracer to facilitate the use of the lowest possible dose and minimize maternal and fetal exposure.³¹ Blue dye is avoided due to the risk of anaphylaxis and other allergic reactions, regardless of the guideline source.⁴³

Indocyanine green (ICG), which does not cross the placenta, is emerging as a tracerless alternative but requires prospective validation in pregnancy.⁴⁴ To date, only a single case report has described the use of TAD in PrBC, in which a patient with HER2-positive cT2N3a breast cancer diagnosed at 22 weeks of gestation underwent nipple-sparing mastectomy with TAD of clipped nodes following neoadjuvant chemotherapy, achieving complete axillary response and avoiding ALND; prospective validation in the pregnant population is lacking.⁴⁵

Venous thromboembolism (VTE) is potentially a fatal surgical complication in PrBC. A nationwide cohort study of 3,581,214 pregnancies demonstrated that cancer diagnosed during pregnancy is associated with a markedly elevated VTE risk: 75.2 per 10,000 pregnancies in women with cancer versus 10.7 per 10,000 in the no-cancer group, representing an approximately sevenfold increase in risk.⁴⁶ Thromboprophylaxis with low-molecular-weight Heparin should be administered.⁹

The safe and effective surgical management of PrBC requires an institutional infrastructure that extends well beyond the operating room. Surgery should occur only in centers with on-site obstetric and neonatal intensive care support, intraoperative fetal monitoring capability, and a dedicated multidisciplinary team meeting (MDT) structure specifically addressing pregnancy-related malignancies.⁹

Conclusion

Breast cancer during pregnancy is a condition that affects both the mother and the fetus and poses serious challenges in diagnosis and treatment management. The primordial principle underpinning this review is that the pregnant context cannot justify therapeutic conservatism at the expense of oncological adequacy. When PrBC is treated with full oncological intent, the pregnancy itself does not independently determine prognosis. Achieving this standard for every patient with PrBC requires institutional commitment, multidisciplinary collaboration, and continued investment in the prospective evidence base.

Declarations

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Table 1. Recommended surgical approaches by gestational trimester in PrBC.

Trimester	Preffered Surgical Approach	Key Considerations
First (≤12 weeks)	Mastectomy preferred; BCS can be considered if adjuvant chemotherapy is planned and RT can be delayed until postpartum(NCCN).	Organogenesis ongoing, RT cannot be given, risk of miscarriage from anesthesia; immediate reconstruction deferred.
Second (13-24 weeks)	BCS or mastectomy; SLNB (Tc99m); neoadjuvant chemotherapy may enable downstaging	Safest anesthetic window; BCS feasible when RT delay until postpartum is clinically acceptable; ALND if SN+; reconstruction deferred.
Third (≥25 weeks)	BCS feasible; mastectomy if BCS margins uncertain	Postpartum RT after delivery without delay; coordinate delivery timing with surgical team; avoid chemo after 35 weeks.

BCS: Breast conserving surgery, RT: radiotherapy, ALND: axillary lymph node dissection.

Review Article

SEXOLOGICAL ASPECTS
OF INFERTILITY**LEVAN KOBALADZE, MD, MPA***Center for Reproductive Medicine "Universe", Tbilisi, Georgia*

ABSTRACT

Background: The diagnosis of infertility and its subsequent prolonged medical procedures induce a severe psycho-emotional crisis within couples. While clinical focus predominantly shifts toward reproductive disorders, their evaluation, and treatment, statistics indicate that over 50% of couples face serious sexual problems in their intimate lives. This article aims to elucidate the bidirectional "vicious cycle" between infertility and sexological disorders, exploring the underlying mechanisms and offering strategic interventions to address these challenges.

Results: The aforementioned issue must be reviewed through two primary dimensions:

1. Sexological Barriers as a Cause of Infertility: In women, conditions such as vaginismus and dyspareunia physically impede penetration and intravaginal ejaculation. In men, erectile dysfunction, anejaculation, retrograde ejaculation, and premature ejaculation obstruct sperm transport to the oocyte, while hypoactive sexual desire reduces the probability of timing the brief "fertile window."

2. Infertility Stress as a Cause of Sexual Dysfunction: Scheduled or "calendar-driven" intercourse eliminates spontaneity. In men, this triggers "performance anxiety", an adrenaline cascade that constricts blood vessels, causing erectile failure; also, in the future, it causes a decrease in libido. In women, hyper-control inhibits the parasympathetic nervous system, disrupting vaginal lubrication and causing anorgasmia. This state is further compounded by a damaged body image and associated psychological complexes.

Conclusion

Breaking this vicious cycle requires a comprehensive, multidisciplinary approach: diversifying intimacy (establishing "non-reproductive" days to alleviate penetration pressure), reframing communication to mitigate individual guilt, and integrating sexological counseling alongside reproductive therapies. Maintaining sexual health during infertility treatments is paramount to preserving partnership cohesion and is frequently a vital prerequisite for overcoming the core issue of infertility itself.

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Keywords: dyspareunia; erectile dysfunction; hypoactive sexual desire; infertility; performance anxiety; premature ejaculation; retrograde ejaculation; vaginismus.

When a couple faces a diagnosis of infertility, their lives change in an instant. Medical offices, endless laboratory and instrumental examinations, and various forms of therapy become a part of their daily routine. On this challenging journey, all focus shifts to reproductive anatomy – eggs, spermatozoa, hormone levels, and the diagnosis and treatment of infections. However, in this process, one vital yet taboo side almost always remains in the shadows – the couple’s sexual life. Infertility is not merely a physiological reality; it is a profound psychological and emotional crisis that directly damages partners’ intimacy.¹ International research shows that more than 50% of couples facing infertility experience serious discomfort in their intimate lives or sexual dysfunctions. Despite this, it is rarely spoken about out loud.²⁻⁵

This is where a so-called “vicious cycle” most commonly forms; sexological problems and infertility are tightly interconnected: on the one hand, certain sexological disorders may physically hinder conception, while on the other hand, the infertility diagnosis itself and the exhausting, prolonged wait to have a child destroy a previously entirely healthy sexual life.⁵⁻⁶

When sex loses its primary functions – pleasure, relaxation, and emotional connection – and becomes a “mechanical chore” scheduled by a calendar, the couple comes under immense psychological pressure. To break this cycle, it is essential to understand the neurobiological and psychological mechanisms hidden behind these issues in both men and women.

When Sexological Issues Cause Infertility (The Cause)

Often, when a couple is unable to achieve pregnancy over a span of years, the cause lies not in hormonal imbalance or anatomical pathologies, but rather in sexological barriers that physically prevent complete sexual intercourse. These are cases where reproductive potential exists, but its realization is blocked at the level of genital intercourse.

The Female Factor: Vaginismus and Dyspareunia

In women, the process of conception is most commonly hindered by two sexological issues:

- **Vaginismus:** This is an involuntary, painful spasm of the pelvic floor and circumvaginal muscles during every attempt at sexual intercourse. During vaginismus, penetration becomes physically impossible. A couple may have a loving relationship for years, yet be unable to engage in vaginal sex. Consequently, sperm cannot enter the vagina, which precludes natural conception.
- **Dyspareunia:** Pain during intercourse can be caused by organic factors (e.g., endometriosis, inflammatory processes) as well as psychogenic causes. The persistent fear of pain forces a woman to avoid intimate contact subconsciously, or leads to intercourse being terminated prematurely so that ejaculation occurs outside the vagina.⁹⁻¹²

The Male Factor: Erectile and Ejaculatory Disorders

On the male side, conception requires a firm erection and ejaculation deep within the vagina. Several disorders can impede this process:

- **Chronic Erectile Dysfunction:** The inability to achieve or maintain an erection until the completion of intercourse directly blocks the possibility of conception, as sperm cannot be transported to the cervix;

- **Anejaculation:** A condition in which a man achieves orgasm and experiences the corresponding pleasurable sensations, yet no physical ejaculation of sperm occurs at all;
- **Retrograde Ejaculation:** In this condition, sperm is not ejaculated externally; instead, due to the malfunction of the bladder sphincter, it travels backward into the urinary bladder;
- **Premature Ejaculation (Ante Portam):** A severe form of premature ejaculation that occurs immediately prior to penetration, as the penis touches the vaginal introitus. In such cases, the vast majority of spermatozoa end up outside the vagina and fail to reach their target.^{13,14}

Hypoactive Libido (Marked Decrease in Sexual Desire)

If either partner (or both) suffers from a chronic lack of sexual desire and intimate contact occurs only once a month or every few months, the mathematical probability of hitting the “fertility window” drops significantly. In the female body, the egg remains viable for only 12–24 hours after ovulation; thus, low sexual frequency can miss this short window of opportunity.

When Infertility Destroys Sexual Life (The Outcome)

This is the second, equally painful side of the coin. When a couple is diagnosed with infertility, and prolonged treatment begins, sex often loses its natural charm and turns into a source of stress.^{2,5,6}

“Calendar Sex” and the Loss of Passion

As soon as the reproductologist tells the couple: “Your optimal days are the 12th, 14th, and 16th of the month,” spontaneity, playfulness, and romance instantly disappear from sex. Intercourse becomes a mechanical task scheduled on a calendar. Partners no longer view sex as a means of bonding and pleasure, but rather as a process of “submitting biological material.”

The Male Mechanism: Performance Anxiety

This phenomenon best illustrates how the mind controls the body. When a man feels the pressure that “today is that unique chance which must not be ruined,” the anxiety center in his brain is activated:^{13,14}

- **Pressure of Responsibility** (Emotional Trigger): The man realizes that today is the day of ovulation and he is “obligated” to perform. The fear arises: “What if I fail?”
- **Adrenaline Cascade** (Physiological Reaction): In response to anxiety, the body produces stress hormones – adrenaline and noradrenaline;
- **Vasoconstriction:** These hormones cause peripheral blood vessels to constrict immediately. Blood flow is redirected to muscles and the heart instead of the genitalia (as the body prepares for a “defense”);
- **Loss of Erection** (Outcome): Due to the blockage of blood flow, the erection instantly fades or fails to occur at all, resulting in situational erectile dysfunction.

The Female Mechanism: Inhibition of Lubrication and Anorgasmia

In women, the stress of infertility directly impacts physical arousal. When a woman thinks only about “whether or not she will get pregnant this time” during sex, her limbic system (the brain’s emotional center) blocks the parasympathetic nervous system.

It is precisely this system that is responsible for the secretion of vaginal lubrication by the Bartholin glands during sexual arousal. Consequently:

- Intercourse becomes dry and physically painful;
- The woman loses the ability to achieve orgasm (anorgasmia), as her mind is in a state of hyper-control rather than relaxation.

Impairment of Body Image

Prolonged infertility generates a feeling in individuals (especially women) that their body is “insufficient,” “defective,” or “not working as it should.” This leads to a loss of faith in one’s attractiveness. A woman develops feelings of shame and insecurities, losing the desire for erotic play or to be nude in front of her partner.⁹⁻¹²

How to Break the Vicious Cycle? (Recommendations)

During infertility treatment, a couple must not allow their intimate life to break down, as a healthy sexual connection is the very pillar that helps them navigate this stress.^{15,16}

Step	Practical Action	Why is it Important?
Diversification of Sex	Establish “non-reproductive” days. Engage in sexual activity outside the ovulation window where penetration is off-limits – use only massage, oral, or manual stimulation.	This relieves “performance anxiety” in men and restores pure pleasure for both partners.
Changing the Language of Communication	Use the formula “our problem” rather than “your problem.” Avoid telling your partner that today is an “obligatory” day. Try initiating it through flirting instead.	Reduces feelings of guilt and psychological pressure.
Multidisciplinary Approach	Alongside visits to a reproductologist, consult a qualified sexologist.	Helps the couple overcome psychogenic (stress-induced) infertility.

Conclusion

Sexual health and reproductive function are two parts of a single whole. The desire and idea of having a child should not sacrifice the love, passion, and attraction that brought the couple together in the first place. Protecting intimate life from mechanical schedules, offering emotional support to one another, and speaking openly about issues are the key factors for a couple to walk this challenging path not distant and alienated, but closer and stronger together.

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20TH WORLD CONGRESS ON HUMAN REPRODUCTION

SHERATON GRAND TBILISI METECHI PALACE

18-21 September, 2025

Tbilisi, Georgia

SCIENTIFIC PROGRAMME

Thursday, 18 September, 2025

REGISTRATION	16:00
OPENING CEREMONY Moderator: Nugzar Rukhadze (GE)	KAVKASIONI BALLROOM 17:00-18:00
Prof. A. Khomasuridze (GE), Introduction Mr. M. Sarjveladze (GE), Minister of Health of Georgia, Greetings Prof. A. Genazzani (IT), Opening Remarks	
OPENING LECTURE Chairpersons: Andrea Genazzani (IT), Archil Khomasuridze (GE)	KAVKASIONI BALLROOM 18:00-18:40
18:00-18:30	Joseph Schenker (IL) International Academy of Human Reproduction – Half Century Activities
18:30-18:40	Natalia Khonelidze (GE) Current State of IVF in Georgia: Trends and Challenges
POSTER SESSION	POSTER AREA (MTIRALA-SHINO) 18:50-20:00

Friday, 19 September, 2025, 17:00-20:00

REGISTRATION				08:00-08:30
	SHKHARA	USHBA	TETNULDI	
08:30	SYMPOSIUM	ACADEMY FOCUS	SYMPOSIUM	
10:00	Assisted Reproductive Technologies	Menopausal Hormone Therapy	Navigating Intrapartum Complications	
10:15	PLENARY SESSION	SYMPOSIUM	SYMPOSIUM	
11:45	Fertility Preservation	Neuroendocrinology and Treatment of Menstrual Disorders	Endometriosis in Reproductive Medicine	
11:45-12:15 Coffee break				

	SHKHARA	USHBA	TETNULDI
12:15 13:45	SYMPOSIUM Surgery and Infertility	PLENARY SESSION Endocrine and Immune Challenges in Pregnancy	SYMPOSIUM Endometriosis, Adenomyosis, Endometrial Challenges
14:00 15:30	ACADEMY FOCUS Challenges in Reproductive Medicine	PLENARY SESSION Polycystic Ovary Syndrome in Focus	PLENARY SESSION Violence, Women Health, Pregnancy Loss

11:45-12:15 *Coffee break*

16:00 17:30	SYMPOSIUM Genetic Testing: What's new?	ACADEMY FOCUS Adolescence Gynecology	SYMPOSIUM Uterine Pathologies and Reproductive Function
17:45 18:15	KEY LECTURE Shantha Kumari (IN) Gender-Based Violence and Reproductive Health	KEY LECTURE Alessandro Genazzani (IT) New Insights on Insulin Resistance in PCOS	KEY LECTURE Wolfgang Holzgreve (DE) Stem Cells in Obstetrics and Prenatal Medicine: An Update
18:30 20:00	GENERAL ASSEMBLY OF IAHR (Academicians only)		

Friday, 19 September, 2025, 08:30-10:00

SYMPOSIUM Assisted Reproductive Technologies Chairpersons: Xiangyan Ruan (CN), Nino Museridze (GE)		SHKHARA 08:30-10:00
08:30-08:50	Zion Ben Rafael (IL) Do We Have Any Proof for the Use of Add-Ons for IVF	
08:50-09:10	Gunay Sultanova (AZ) Successful IVF Procedure in a Woman with a Unicornuate Uterus in Our Clinic Experience	
09:10-09:30	Xiangyan Ruan (CN) New Experience in Technique and Clinic of Ovarian Tissue Cryopreservation and Transplantation [From the First Ovarian Tissue Cryobank in China]	
09:30-09:50	Oliko Murgulia (GE) Phenotypic features of chronic endometritis, persistence and progression molecular markers	
09:50-10:00	<i>Discussion</i>	

ACADEMY FOCUS	USHBA
Menopausal Hormone Therapy	08:30-10:00
Chairpersons: Anne Gompel (FR), Vladislav Korsak (RU)	

- 08:30-08:55 Alfred Mueck (DE) Choice of the Progestogen for MHT in Menopausal Women
- 08:55-09:20 Anne Gompel (FR) Menopause Hormone Treatment and Breast Cancer Risk/ The Unique Risk of MHT is Breast Cancer?
- 09:20-09:45 Andrea Genazzani (IT) Adrenopause and Menopause and Women Ageing: Effects of DHEA Alone and Combined with MHT Therapies
- 09:45-10:00 Discussion

SYMPOSIUM	TETNULDI
Navigating Intrapartum Complications	08:30-10:00
Chairpersons: David Bokhua (DE), Ⴓ (GE)	

- 08:30-08:50 Gulnara Asymbekova (KG) Long-term Outcomes for Children Following Intrapartum Complications: Analysis of Leading Risk Factors in High-Risk Women, Including Those Undergoing IVF
- 08:50-09:10 Tinatin Gagua (GE) Premature Rupture of Membranes – Challenges and Management
- 09:10-09:30 Lali Melia (GE) Strategies of the Prevention of Preterm Delivery
- 09:30-09:50 David Davarashvili (GE) Does a Short Cervix Mean Cervical Insufficiency
- 09:50-10:00 Discussion

Friday, 19 September, 2025, 10:15-11:45

PLENARY SESSION	SHKHARA
Fertility Preservation	10:15-11:45
Chairpersons: Zion Ben Rafael (IL), Gian Carlo Di Renzo (IT)	

- 10:15-10:35 Keteven Osidze (GE) Implantation of Embryo-Expectations vs. Practice
- 10:35-10:55 Nino Museridze (GE) Biological Age of Women and Ways to Preserve Fertility
- 10:55-11:15 Ludmila Barbakadze (GE) Fertility Preservation: Current Trends, Challenges, and Opportunities
- 11:15-11:35 Irakli Todua (GE) Fertility Options in Young Patients with Ovarian Cancer
- 11:35-11:45 Discussion

SYMPOSIUM of the EUROPEAN SOCIETY of GYNECOLOGY	USHBA
Neuroendocrinology and Treatment of Menstrual Disorders	10:15-11:45
Chairpersons: Camil Castelo-Branco (ES), Nino Davidova (GE)	

- 10:15-10:40 Blazej Meczekalski (PL) Neuroendocrine Background of Functional Hypothalamic Amenorrhea (FHA)
- 10:40-11:05 Alessandro Genazzani (IT) The Use of Low-Dose Estrogens as Treatment for Functional Hypothalamic Amenorrhea (FHA)
- 11:05-11:30 Lali Pkhaladze (GE) Reasonable and Rational Therapy of Menstrual Disorders
- 11:30-11:45 Discussion

SYMPOSIUM

Endometriosis in Reproductive Medicine

TETNULDI

10:15-11:45

Chairpersons: **Martin Birkhauzer** (CH), **Marika Jafaridze** (GE)

- 10:15-10:35 David Bokhua** (DE) Surgical Treatment of Patients with Deep Infiltrating Endometriosis (DIE) of the Bowel or Bladder
- 10:35-10:55 David Skhirtladze** (GE) Efficacy of Combined Surgical and Hormonal Therapy for Infertile Patients with Deep Endometriosis
- 10:55-11:15 Paata Zhorzholiani** (GE) Balloon Occlusion and Stenting of Iliac Arteries. Technique and Advantages of B-Lynch Compression Sutures
- 11:15-11:35 Lela Iremadze** (GE) Pregnancy Rates After Laparoscopic and IVF Treatments of Minimal or Mild Endometriosis – 10 Years' Experience
- 11:35-11:45 Discussion**
- 11:45-12:15 Coffee break**

Friday, 19 September, 2025, 12:15-13:45

SYMPOSIUM

Surgery and Infertility

SHKHARA

12:15-13:45

Chairpersons: **Klaus Diedrich** (DE), **Ketevan Osidze** (GE)

- 12:15-12:35 Liselotte Mettler** (DE) Infertility Surgery in 2025
- 12:35-12:55 Klaus Diedrich** (DE) The Use of GnRH Antagonists for Ovarian Stimulation
- 12:55-13:15 Arsen Gvenetadze** (GE) Hysteroscopic Septectomy in RPL Patients, Our Clinical Experience
- 13:15-13:35 Archil Chkhotua** (GE) Recurrent UTI in Women. Impact on Fertility
- 13:35-13:45 Discussion**

PLENARY SESSION

Endocrine and Immune Challenges in Pregnancy

USHBA

12:15-13:45

Chairpersons: **Frank Chervenak** (US), **Nino Davidova** (GE)

- 12:15-12:35 Natia Vashakmadze** (GE) Thyroid and Pregnancy – a Journey from Physiology to Pathology
- 12:35-12:55 Tea Khurodze** (GE) Gestational Diabetes Mellitus: Screening and Management"
- 12:55-13:15 Ketevan Gotsiridze** (GE) The Role of pNK Cells and Cytokines in Recurrent Pregnancy Loss and Regulation of Their Level by KIR Receptors
- 13:15-13:35 Marina Jangidze** (GE) New Approaches to the Management of Pregnant Women with Antiphospholipid Syndrome and Genetic Forms of Thrombophilia Against the Background of Myeloproliferative Diseases
- 13:35-13:45 Discussion**

SYMPOSIUM of the EUROPEAN SOCIETY of GYNECOLOGY	TETNULDI
Endometriosis, Adenomyosis, Endometrial Challenges	12:15-13:45
Chairpersons: Camil Castelo-Branco (ES), Blazej Meczekalski (PL)	

12:15-12:40	Giuseppe Benagiano (IT) Are Adenomyosis & Endometriosis Different Manifestations of the Same Disorder?
12:40-13:05	Tevfik Yoldemir (TR) ART Outcomes in Women with Endometriosis and Adenomyosis
13:05-13:30	Lali Pkhaladze (GE) Thin Endometrium - Therapeutic Potential of Enzyme-Based Therapy
13:30-13:45	Discussion

Friday, 19 September, 2025, 14:00-15:30

ACADEMY FOCUS	SHKHARA
CHALLENGES IN REPRODUCTIVE MEDICINE	14:00-15:30
Chairpersons: Lika Chkonia (GE), Joseph Schenker (IL)	

14:00-14:25	Klaus Diedrich (DE) Fertility Preservation in Cancer Patients. Preimplantation Diagnosis: The Difficult Development in Germany
14:25-14:50	Liselotte Mettler (DE) Uterine Preserving Surgeries in Infertility Patients
14:50-15:15	Teimuraz Gagnidze (GE) Sperm DNA Fragmentation in Male Partners of Couples with Unexplained Infertility and Recurrent Pregnancy Loss in Georgia
15:15-15:30	Discussion

PLENARY SESSION	USHBA
Polycystic Ovary Syndrome in Focus	14:00-15:30
Chairpersons: George Creatsas (GR), Natalia Khonelidze (GE)	

14:00-14:20	Seang Lin Tan (CA) PCOS and Long-Term Health Outcome on Women and Children
14:20-14:40	Lali Pkhaladze (GE) PCOS Phenotypes: A new Lens On an Old Syndrome
14:40-15:00	Elene Asanidze (GE) Genetic and Metabolic Impact in PCOS: MTHFR Polymorphisms, Homocysteine, Insulin-Resistance and Pregnancy Outcome
15:00-15:20	Xiangyan Ruan (CN) Managing PCOS Patients in the Worldwide Largest Department of Gynecological Endocrinology
15:20-15:30	Discussion

PLENARY SESSION	TETNULDI
Violence, Women’s Health, Pregnancy Loss	14:00-15:30
Chairpersons: Gian Carlo Di Renzo (IT), Wolfgang Holzgreve (DE)	

14:00-14:20	Vladislav Korsak (RU) Reproductologists, Remember About Obstetricians!
14:20-14:40	Frank Chervenak (US) Obstetric Violence: A Misnomer?
14:40-15:00	Shantha Kumari (IN) Violence Against Women. What is Our Role as OB-GYNs?
15:00-15:20	Lali Melia (GE) Management of Early Pregnancy Loss: What works today?
15:20-15:30	Discussion
15:30-16:00	Coffee break

Friday, 19 September, 2025, 16:00-17:30

SYMPOSIUM	SHKHARA
Genetic Testing: What’s new?	16:00-17:30
Chairpersons: Vyacheslav Lokshin (KZ), Maka Chipashvili (GE)	

- 16:00-16:25 Ketevan Tukhashvili (GE) Non-Invasive Preimplantation Genetic Testing
- 16:25-16:50 Lali Kharabadze (GE) The Ultrafast Warming Protocol – Where Are We Now?
- 16:50-17:15 Maka Chipashvili (GE) Reproductive Genetic Advances: Solutions or New Challenges?
- 17:15-17:30 Discussion

ACADEMY FOCUS	USHBA
Adolescence Gynecology	16:00-17:30
Chairpersons: George Creatsas (GR), Jenaro Kristesashvili (GE)	

- 16:00-16:25 Johannes Bitzer (CH) How to Understand the Adolescent Brain
- 16:25-16:50 George Creatsas (GR) Vaginal Aplasia. Creatsas Vaginoplasty
- 16:50-17:15 Blazej Meczekalski (PL) PCOS in Adolescents - Current View
- 17:15-17:30 Discussion

SYMPOSIUM	TETNULDI
Uterine Pathologies and Reproductive Function	16:00-17:30
Chairpersons: Gulnara Asymbekova (KG), Ludmila Barbakadze (GE)	

- 16:00-16:20 Maka Gegechkori (GE) Benign Uterine Diseases and Associations with Reproductive Function
- 16:20-16:40 George Tevdorashvili (GE) The Latest Standards of Modern Diagnostics and Clinical Practice of Uterine Pathologies
- 16:40-17:00 Madona Jugheli (GE) Integrated PCR-Based Profiling of the Entire Female Reproductive Microbiome: Diagnostic Accuracy & Clinical Correlates
- 17:00-17:20 Nato Shamugia (GE) The Importance of Uterine Microbiome and Implantation Window Correction for Embryo Transfer
- 17:20-17:30 Discussion

Friday, 19 September, 2025, 17:45-18:15

KEY LECTURE	SHKHARA
Chairpersons: Tevfik Yoldemir (TR), Arsen Gvenetadze (GE)	17:45-18:15

Shantha Kumari (IN) Gender-Based Violence and Reproductive Health

KEY LECTURE	USHBA
Chairpersons: Gamal Serour (EG), Seang Lin Tan (CA)	17:45-18:15

Alessandro Genazzani (IT) New Insights on Insulin Resistance in PCOS

KEY LECTURE	TETNULDI
Chairpersons: Frank Chervenak (US), Alfred Mueck (DE)	17:45-18:15

Wolfgang Holzgreve (DE) Stem Cells in Obstetrics and Prenatal Medicine: An Update

GENERAL ASSEMBLY OF THE INTERNATIONAL ACADEMY OF HUMAN REPRODUCTION
(Academicians only)

TETNULDI
18:30-20:00

GALA DINNER

MTATSMINDA PLATEAU, 9, Qaqutsa Cholokashvili str., Tbilisi
20:00

Friday, 19 September, 2025, 17:45-18:15

REGISTRATION

08:00-08:30

	SHKHARA	USHBA	GERGETI	TETNULDI	MTIRALA-SHINO
08:30 10:00	SYMPOSIUM Challenging Issues in Reproductive Medicine	SYMPOSIUM Environment and Reproductive Function	ORAL PRESENTATION Advances in Reproductive Medicine	SESSION -INFERTILITY 35+ Opening Ceremony and Opening Lecture	
10:15 11:45	SYMPOSIUM Achievements and Challenges in IVF	SYMPOSIUM Adolescent Pregnancy and Contraception	ORAL PRESENTATION Challenges in Ob/Gyn and Reproductive Medicine	SESSION -INFERTILITY 35+ Management of Infertility in Couples Aged 35 and Older	SESSION -INFERTILITY 35+ Management of Infertility in Couples

11:45-12:15 *Coffee break*

12:15 13:45	SYMPOSIUM Embryology in Reproductive Medicine	PLENARY SESSION Normal and Abnormal Sexual Development	PLENARY SESSION Reproductive Healthcare	SESSION -INFERTILITY 35+ Managing Challenging IVF Patients: Clinical and Communicative Strategies	SESSION -INFERTILITY 35+ Managing Challenging IVF Patients: Clinical and Communicative Strategies
14:00 15:30	SYMPOSIUM Ethics and Artificial Intelligence in Reproductive Health	SYMPOSIUM Sexual Disfunction	ACADEMY FOCUS Oncological Risks in Reproductive Medicine	SESSION -INFERTILITY 35+ IVF; Genetic	SESSION -INFERTILITY 35+ IVF; Genetic

15:30-16:00 *Coffee break*

	SHKHARA	USHBA	GERGETI	TETNULDI	MTIRALA-SHINO
16:00 17:30	ACADEMY FOCUS IVF Laboratory and Novel Genetic Screening Methods	ORAL PRESENTATION Adolescence: Norma and Abnormality	ORAL PRESENTATION Optimising Reproductive Healthcare	SESSION -INFERTILITY 35+ Embryology 17:00- 17:30 Nino Museridze's Book Presentation	SESSION -INFERTILITY 35+ Embryology
17:45 18:15	KEY LECTURE Gamal Serour (EG) Impact of Religion, Culture, and Ethics on ART Practices	KEY LECTURE Andrea Genazzani (IT) Brain and Mood as Target of Hormonal Contraception: A Matter of Individual Vulnerability	KEY LECTURE Seang Lin Tan (CA) Demographic Decline and Its Global Implications, and Possible Solutions	SESSION -INFERTILITY 35+ Embryology 17:00- 17:30 Nino Museridze's Book Presentation	SESSION -INFERTILITY 35+ Embryology
18:30 20:00	GENERAL ASSEMBLY OF IAHR (Academics only)				

Saturday, 20 September, 2025, 08:30-10:00

SYMPOSIUM		SHKHARA
Challenging Issues in Reproductive Medicine		08:30-10:00
Chairpersons: Tevfik Yoldemir (TR), Ludmila Barbakadze (GE)		
08:30-08:50	Victor Gomet (CA) Robert Edwards – The Man and Vision	
08:50-09:10	Tatiana Nazarenko (RU) Possibilities for Improving IVF Outcomes in Women with Unexplained Infertility and Diminished Ovarian Reserve	
09:10-09:30	Vyacheslav Lokshin (KZ) Unsolved Issues of Modern Reproductive Medicine	
09:30-09:50	Tamar Giorgadze (GE) Cesarean Scar Niche: Advances in Diagnosis and Management	
09:50-10:00	<i>Discussion</i>	

SYMPOSIUM	USHBA
Environment and Reproductive Function	08:30-10:00
Chairpersons: Alessandro Genazzani (IT), Lali Pkhaladze (GE)	

08:30-08:55	Camil Castelo-Branco (ES) Endocrine Disruptors. The Need of Common Sense
08:55-09:20	Gian Carlo Di Renzo (IT) Effect of Environment and Nutrients on Fertility, Reproduction and Pregnancy
09:20-09:45	Mari Malazonia (GE) Nutrition, Reproduction and Age
09:45-10:00	Discussion

ORAL PRESENTATION	GERGETI
Advances in Reproductive Medicine	08:30-10:00
Chairpersons: Nani Marsagishvili (GE), David Skhirtladze (GE)	

08:30-08:39	Nino Nadiradze (GE) The Growing Role of GLP-1 RAs for the Management of PCOS
08:39-08:48	Mariam Shervashidze (GE) Pregnancy Rate in the Case of Mosaic Embryo Transfer
08:48-08:56	Hripsime Grigoryan (AM) Premature Ovulation During COH for IVF Patients with Low Ovarian Reserve: Cancelled cycle or.....
08:56-09:05	Ketevan Shengelaia (GE) Features of Androgen Receptor Expression in Ovarian and Breast Epithelial Cancer, Apoptotic and Stem Cell
09:05-09:14	Natavan Akhundova (AZ) Features of Hormonal Changes in Reproductive-Aged Women with Hyperandrogenism Syndrome
09:14-09:23	Nino Maisuradze (GE) Follicular Fluid: A Window into Oocyte Health and IVF Success
09:23-09:32	Lida Khachatryan (AM) Letrozole in the Practice of Reproductologist
09:32-09:41	Yuejiao Wang (CN) Serum microRNA-181a Expression Level in Breast Cancer Patients and Its Correlation with Circulating PGRMC1
09:41-09:50	Magda Tortladze (GE) Reproductive Tourism in Georgia: International Surrogacy Practices and the Domestic Legal Landscape
09:50-10:00	Discussion

Session Infertility 35+

REGISTRATION	08:00-08:30
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GREETINGS	TETNULDI
Opening Ceremony	08:30-09:00
Chairpersons: Andrea Genazzani (IT), Archil Khomasuridze (GE), Nino Museridze (GE)	

08:30-08:40	Prof. Andrea Genazzani (IT) Introduction
08:40-08:50	Prof. Archil Khomasuridze (GE) Greetings
08:50-09:00	Prof. Nino Museridze (GE) Opening Remarks

PLENARY SESSION OF INFERTILITY 35+

TETNULDI

Opening Lecture

09:00-10:00

Chairpersons: **Andrea Genazzani** (IT), **Nino Museridze** (GE)

- 09:00-09:12 **Diego Excurra** (US) Details of the Advancement of Global Fertility Technologies Around the World
- 09:12-09:24 **Zaza Bokhua** (GE) Postgraduate Medical Education and Continuous Professional Development in Reproductive Health
- 09:24-09:36 **David Kereselidze** (GE) To Value the Well-Being of the Patient and Potential Offspring as Paramount
- 09:36-09:48 **Nino Museridze** (GE) Technological Advancements and Opportunities in Georgia (Recent Innovations, Areas where We Outperform Other Countries and the Presence of a Favourable Legal Environment)
- 09:48-10:00 *Discussion*

Saturday, 20 September, 2025, 10:15-11:45

SYMPOSIUM

SHKHARA

Achievements and Challenges in IVF

10:15-11:45

Chairpersons: **Vyacheslav Lokshin** (KZ), **Lika Chkonia** (GE)

- 10:15-10:35 **Tamar Barbakadze** (GE) Role of Endometrial Receptivity Analysis in Enhancing ART Outcomes for Advanced-Age Patients
- 10:35-10:55 **Ani Morchiladze** (GE) The Role of IVF in Treatment of Infertility Associated with Endometriosis
- 10:55-11:15 **Ketevan Osidze** (GE) Surrogacy – Almost Ideal Clinical Model to Test Embryo Potential
- 11:15-11:35 **Vyacheslav Lokshin** (KZ) Infertility After 40: A Challenge for Modern Medicine
- 11:35-11:45 *Discussion*

SYMPOSIUM

USHBA

Adolescent Pregnancy and Contraception

10:15-11:45

Chairpersons: **Archil Khomasuridze** (GE), **Teimuraz Gagnidze** (GE)

- 10:15-10:40 **Johannes Bitzer** (CH) Contraception for Patients with Psychiatric Disorders
- 10:40-11:05 **Martin Birkhauser** (CH) Hormonal Contraception: Effect on Peak Bone Mass
- 11:05-11:30 **George Creatsas** (GR) Adolescent Pregnancy and Contraception
- 11:35-11:45 *Discussion*

ORAL PRESENTATION		GERGETI
Challenges in Ob/Gyn and Reproductive Medicine		10:15-11:45
Chairpersons: George Tevdorashvili (GE), Maka Jorbenadze (GE)		
10:15-10:24	Anna Gvenetadze (GE) Management of RPL and Pregnancy Outcomes	
10:24-10:33	Ana Chlaidze (GE) Impact of the Pregnancy and Labour Risk Factors on the Development of Autistic Spectrum Disorder	
10:33-10:42	Nunu Razmadze (GE) Adipose Tissue and Reproductive Health: Mechanistic Insights and Clinical Implications in Overweight and Obese Patients	
10:42-10:51	Natalia Rusakova (GE) Effectiveness of Lymphocyte Immunotherapy in Obstetrics, Gynecology and Reproductology	
10:51-11:00	Kristina Melikyan (AM) IVG in Patients with Chronic Endometritis: Does the Adjuvant Therapy Affect the Implantation?	
11:00-11:09	Nino Ustiashvili (GE) The Immunology of Endometriosis. How the Immunology Knowledge is Shaping Management Strategies	
11:09-11:18	Nutsa Chighladze (GE) Pregnancy Following Craniopharyngioma Resection and Pituitary Atrophy: A Rare Case Report	
11:18-11:27	Mariam Andghuladze (GE) The Role of GABAergic Dysregulation in PCOS and FHA: Shared Neuroendocrine Pathways and Divergent Clinical Manifestations	
11:27-11:36	Dina Martirosyan (AM) Effectiveness of Progesterone in PPOS Protocols. Are the All Progesterones Equal?	
11:36-11:45	<i>Discussion</i>	

SESSION – INFERTILITY 35+		TETNULDI
Management of Infertility in Couples Aged 35 and Older		10:15-11:45
Chairpersons: Diego Excurra (US), Zaza Bokhua (GE), Nino Museridze (GE)		
10:15-10:35	Raul Orvieto (IL) Fresh vs. Freeze – All Cycles – When and To Whom? Reproductive Specificities in Women Over 35 Ido	
10:35-10:55	Ben Ami (IL) GnRH Antagonists vs. Progestins – Is It Time to Change?	
10:55-11:15	Tamara Nadirashvili (GE) Management Specifics of Surrogacy and Donation Programs	
11:15-11:35	Mamuka Nemsadze (GE) Nutritional Interventions and Diagnostic Approaches for the Prevention of Preeclampsia	
11:35-11:45	<i>Discussion</i>	

SESSION – INFERTILITY 35+		MTIRALA-SHINO
Management of Infertility in Couples Aged 35 and Older		10:15-11:45
Chairpersons: Tengiz Asatiani (GE), Nato Shamugia (GE)		
10:15-10:35	Gamal Serour (EG) Infertility Management in Women Over 35+	
10:35-10:55	Nato Shamugia (GE) The Importance of Uterine Microbiome and Implantation Window Correction for Embryo Transfer	
10:55-11:15	Marina Gvakharia (US) From Good to Gold Standard: Implementing Quality Systems in IVF Labs	
11:15-11:35	Tea Charkviani (GE) Pregnancy Outcome After Transferring Genetically Tested Embryos vs. Non-Tested Embryos	
11:35-11:45	<i>Discussion</i>	

11:45-12:15 *Coffee break*

Saturday, 20 September, 2025, 12:15-13:45

SYMPOSIUM		SHKHARA
Embryology in Reproductive Medicine		12:15-13:45
Chairpersons: Andreas Schmutzler (DE), Ketevan Osidze (GE)		
12:15-12:35	Temiko Zhorzholadze (GE) Comparison of Two Sperm Processing Methods and Their Impact on Fertilisation, Embryogenesis, and Euploidy Rates	
12:35-12:55	Tamar Kbilashvili (GE) Progesterone Primed Stimulation vs GnRH Antagonists: A Comparative Review	
12:55-13:15	Beqa Sibashvili (GE) Micro-TESE, The Best Surgical Option for the Worst Cases of Non-Obstructive Azoospermia	
13:15-13:35	Sergey Sergeyev (GE) Artificial Intelligence: A “Black Mirror” in Assisted Reproductive Technology	
13:35-13:45	<i>Discussion</i>	

PLENARY SESSION		USHBA
Normal and Abnormal Sexual Development		12:15-13:45
Chairpersons: Anne Gompel (FR), Ani Morchiladze (GE)		
12:15-12:40	Zion Ben Rafael (IL) Why the Research on Decreasing Ovarian Reserve Failed	
12:40-13:05	Jenaro Kristesashvili (GE) X Chromosome Anomalies as a Cause of Non-Iatrogenic Premature Ovarian Insufficiency (POI)	
13:05-13:30	Alla Vash Margatina (US) Mullerian Anomalies: Current Practice and Genetic Landscape (online presentation)	
13:30-13:45	<i>Discussion</i>	

PLENARY SESSION		GERGETI
Reproductive Healthcare		12:15-13:45
Chairpersons: Johannes Bitzer (CH), Eduard Hambartsoumian (AM)		
12:15-12:35	Joseph Schenker (IL) Human Reproduction – Future Goals	
12:35-12:55	Frank Chervenak (US) Reproductive Healthcare at Risk: The Ethical Response to Zealotry and Inequity	
12:55-13:15	Tina Buchholz (DE) Preconceptional Health Care Programs	
13:15-13:35	Zurab Marshania (GE) Complex/Combined Treatment of Women with Vaginismus: Evidence-based Study	
13:35-13:45	<i>Discussion</i>	

SESSION – INFERTILITY 35+	TETNULDI
Managing Challenging IVF Patients: Clinical and Communicative Strategies	12:15-13:45
Chairpersons: Mamuka Nemsadze (GE), Zaza Bokhua (GE), Nino Museridze (GE)	

12:15-12:35	Tamar Antelava (GE) Aspects of Prenatal Care of Singleton Pregnancies
12:35-12:55	Mamuka Nemsadze (GE) Exploring the Endometrium in Cases of Recurrent Implantation Failure
12:55-13:15	Tamar Magularia (GE) Progestogens and Their Role in Realizing and Preserving Reproductive Potential
13:15-13:35	Halyna Strelko (UA) Best Strategies of Egg Donors Preparation
13:35-13:45	Discussion

SESSION – INFERTILITY 35+	MTIRALA-SHINO
Managing Challenging IVF Patients: Clinical and Communicative Strategies	12:15-13:45
Chairpersons: Tengiz Asatiani (GE), Nato Shamugia (GE)	

12:15-12:35	Tengiz Asatiani (GE) High-Risk Pregnancy Management After IVF: Focus on Twin Pregnancies
12:35-12:55	Giorgi Tevdorashvili (GE) Hormonal Correction of Menstrual Cycle Disorders (MCD): Focus on Sex Steroids
12:55-13:15	Maka Gegechkori (GE) Controversies in the Management of Endometrioma – Pros. & Cons
13:15-13:35	Sholpan Karibaeva (KZ) Oocyte Cryopreservation as a Life Strategy: Clinical Outcomes and Patient Emotions
13:35-13:45	Discussion

Saturday, 20 September, 2025, 14:00-15:30

SYMPOSIUM	SHKHARA
Ethics and Artificial Intelligence in Reproductive Health	14:00-15:30
Chairpersons: Joseph Schenker (IL), Giuseppe Benagiano (IT)	

14:00-14:20	Andreas Schmutzler (DE) AI in Reproductive Medicine
14:20-14:40	Eduard Hambartsoumian (AM) Features, Challenges and Success in the Development of Reproductive Medicine in Armenia
14:40-15:00	Victoria Yuzko (UA) OptiPredict IVF: An AI-Powered Platform for Personalised Controlled Ovarian Stimulation – Experience from a Ukrainian Clinic
15:00-15:20	Giuseppe Benagiano (IT) Abortion: Can a Minimum Common Denominator be Found Between “Pro-Choice” and “Pro-Life” groups?
15:20-15:30	Discussion

SYMPOSIUM

USHBA

Sexual Dysfunction

14:00-15:30

Chairpersons: **Johannes Bitzer** (CH), **Elene Asanidze** (GE)

- 14:00-14:25 **Elena Selantieva** (RU) Organic Causes of Female Sexual Dysfunction – The Role of Energy Based Devices
- 14:25-14:50 **Tina Buchholz** (DE) Transgender Care
Levan Kobaladze (GE) Relationship Between Female Sexual Dysfunctions and Gynecological Pathologies
- 14:50-15:15
- 15:15-15:30 *Discussion*

ACADEMY FOCUS

GERGETI

Oncological Risks in Reproductive Medicine

14:00-15:30

Chairpersons: **Seang Lin Tan** (CA), **ᄒ** (GE)

- 14:00-14:25 **Tevfik Yoldemir** (TR) Genetic/Familial High-Risk Assessment: Breast & Ovarian Cancer
- 14:25-14:50 **Anne Gompel** (FR) How to Evaluate the Risk of Breast Cancer?
Roberto Tozzi (IT) Type C2 Nerve Sparing Radical Hysterectomy for IB3 Cervical Cancer: The Two Bridges Technique
- 14:50-15:15
- 15:15-15:30 *Discussion*

SESSION – INFERTILITY 35+

TETNULDI

IVF; Genetic

14:00-15:30

Chairpersons: **Suleyman Aktuna** (TR), **Nino Museridze** (GE)

- 14:00-14:25 **Suleyman Aktuna** (TR) Enhancing PGT-A Success and Minimizing Bias: The Promise of a Premium Approach
- 14:25-14:50 **Maka Chipashvili** (GE) Genetics + Andrology: Genetic Aspects of Male Infertility
- 14:50-15:15 **Volkan Baltaci** (TR) IVF for Genetics: Enhancing IVF Laboratory Monitoring and Safety
- 15:15-15:30 *Discussion*

SESSION – INFERTILITY 35+

MTIRALA-SHINO

IVF; Genetic

14:00-15:30

Chairpersons: **Evrin Unsal** (TR), **Nato Shamugia** (GE)

- 14:00-14:25 **Evrin Unsal** (TR) Enhancing Genetic Diagnosis: Integrating Aneuploidy Screening in PGT Cycles for Improved Clinical Outcomes
- 14:25-14:50 **Yossi Mizrahi** (IL) Fertility Preservation in Women with Turner Syndrome
- 14:50-15:15 **Adva Aizer** (IL) Navigating the Choice Between Early Day 5 or Fully Hatched Day 6 Blastocyst Biopsy for PGT-M (online presentation)
- 15:15-15:30 *Discussion*
- 15:30-16:00 *Coffee break*

Saturday, 20 September, 2025, 16:00-17:30

ACADEMY FOCUS		SHKHARA
IVF Laboratory and Novel Genetic Screening Methods		16:00-17:30
Chairpersons: Liselotte Mettler (DE), Ketevan Gotsiridze (GE)		
16:00-16:20	David McCulloh (US) Frozen euploid single embryo transfer: Factors from retrieval and FET cycle that influence live birth outcomes	
16:20-16:40	Lika Chkonია (GE) Clean Air, Healthy Embryos: Managing Airborne Particulates, Microbes and VOCs in the IVF Laboratory	
16:40-17:00	Wolfgang Holzgreve (DE) Non-Invasive Preimplantation Testing	
17:00-17:20	Oleksiy Pravdyuk (UA) Transfer of Mosaic Embryos: Between Risks and Benefits	
17:20-17:30	Discussion	

ORAL PRESENTATION		USHBA
Adolescence: Norma and Abnormality		16:00-17:30
Chairpersons: Tina Buchholz (DE), Elene Asanidze (GE)		
16:00-16:09	Maka Jorbenadze (GE) Reproductive Health Characteristics of Adolescent Girls in Georgia	
16:09-16:18	Ana Jibladze (GE) Tetrasomy X in an Adolescent Girl	
16:18-16:27	Manana Urjumelashvili (GE) Homocysteine Levels in Patients with PCOS with and without Insulin-Resistance	
16:27-16:36	Tatevik Kirakosyan (AM) Reproductive Help to the Patients After Post-War Traumatic Loss of Children. New Horizons of IVF	
16:36-16:45	Elisabed Pkhaladze (GE) Weight as a Modulator of Hormonal and Metabolic Patterns in Classic PCOS Across Age Groups	
16:45-16:54	Salome Sabulua (GE) Hormonal Interference: Unveiling the Adolescent Spectrum of Hyperprolactinemia	
16:54-17:03	Adrine Grigoryan (AM) Methods of CAH Diagnosis and Treatment. Frequency in the Armenian Population	
17:03-17:12	Mariam Gugushvili (GE) Optimising Gynecological Care in Young Girls and Teens: Challenges and Innovations	
17:12-17:21	Vakhtang Gurabanidze (GE) The Impact of Maternal Obesity on Pregnancy Outcomes: A Cross-Sectional Cohort Study	
17:21-17:30	Discussion	

ORAL PRESENTATION

Optimizing Reproductive Health Care

GERGETI

16:00-17:30

Chairpersons: **Dina Kurdiani (GE)**, **David Skhirtladze (GE)**

- 16:00-16:09** **Manana Mgaloblishvili (GE)** Reconstruction of the Fallopian Tube Using Office Mini Hysteroscopy During Infertility Treatment
- 16:09-16:18** **Ia Chapidze (GE)** Diagnostic Capabilities for Mullerian Anomalies in Women with Reproductive Disorders
- 16:18-16:27** **Margarit Grigoryan (AM)** Indications for Ovarian Peri-Surgical Freezing in Patients with Endometriosis
- 16:27-16:36** **Nino Abesadze (GE)** Vitamin D in fertile women with endometriosis
- 16:36-16:45** **Ana Ghviniashvili (GE)** The Impact of Post-Cesarean Section Isthmocele on Reproductive Health
- 16:45-16:54** **Rusudan Jashi (GE)** Maternal Medication and Neonatal Risk: The Case for Digital Integration
- 16:54-17:03** **Lida Stepanyan (AM)** IVF Programs Optimisation in Patients with Endometriosis: The Analysis of the Environment for Embryo Cultivation
- 17:03-17:12** **Samira Taghieva (AZ)** Modern Approaches to the Treatment of Infertility of Unknown Genesis. Individualisation of Protocols, New Markers, Biomarkers
- 17:12-17:21** **Mariam Tevdorashvili (GE)** Comparative Effectiveness of Short-Course Oral Metronidazole for Bacterial Vaginosis in Reproductive Age Women with Vitamin D Deficiency: With and Without Vitamin D Therapy
- 17:21-17:30** *Discussion*

SESSION – INFERTILITY 35+

Embryology

TETNULDI

16:00-17:00

Chairpersons: **Andrey Kuliev (IL)**, **Maka Chipashvili (GE)**, **Nino Museridze (GE)**

- 16:00-16:15** **Suleyman Aktuna (TR)** Optimising Donor Carrier Screening Strategies for Effective Matching
- 16:15-16:30** **Marina Gvakharia (US)** Error Prevention and Safety in IVF. Title: “Defensive Embryology: Building a Culture of Safety in the IVF Lab”
- 16:30-16:45** **Andrey Kuliev (IL)** Artefacts or Mosaicism? Perfecting PGT-A
- 16:45-17:00** *Discussion*

SESSION – INFERTILITY 35+

TETNULDI

17:00-17:30

Nino Museridze’s Book Presentation

Saturday, 20 September, 2025, 17:45-18:15

KEY LECTURE

SHKHARA

Chairpersons: **Martin Birkhauzer (CH)**, **Liselotte Mettler (DE)**

17:45-18:15

Gamal Serour (EG) Impact of Religion, Culture, and Ethics on ART Practices

KEY LECTURE	USHBA
Chairpersons: Blazej Meczekalski (PL), Giuseppe Benagiano (IT)	17:45-18:15
Andrea Genazzani (IT) Brain and Mood as Target of Hormonal Contraception: A Matter of Individual Vulnerability	
KEY LECTURE	TETNULDI
Chairpersons: Alfred Mueck (DE), Shantha Kumari (IN)	17:45-18:15
Seang Lin Tan (CA) Demographic Decline and Its Global Implications, and Possible Solutions	
GENERAL ASSEMBLY OF THE INTERNATIONAL ACADEMY OF HUMAN REPRODUCTION (Academicians only)	SHKHARA 18:30-20:00
GALA DINNER	MTATSMINDA PLATEAU, 9, Qaqutsa Cholokashvili str., Tbilisi 20:00

Sunday, 21 September, 2025

REGISTRATION		08:00	
	SHKHARA	TETNULDI	MTIRALA-SHINO
08:30	PLENARY SESSION	SESSION - INFERTILITY 35+	SESSION - INFERTILITY 35+
10:00	Menopause and Oncological Diseases in Ob/Gyn	Oncofertility and Surgery	Oncofertility and Surgery
10:15	SYMPOSIUM	SESSION - INFERTILITY 35+	SESSION - INFERTILITY 35+
11:45	Oncology and Reproductive Health	Andrology and Male Fertility	Andrology and Male Fertility
11:45-12:15 <i>Coffee break</i>			
12:15	SYMPOSIUM	SESSION - INFERTILITY 35+	SESSION - INFERTILITY 35+
13:45	From Pubertal Endocrine Disorders to Implantation Success	Gyn+Obstetrics/ART- Related Conditions	Gyn+Obstetrics/ART- Related Conditions
14:00	CLOSING CEREMONY of the 20TH WORLD CONGRESS on		
14:30	HUMAN REPRODUCTION		
15:30		WORKSHOP - INFERTILITY	WORKSHOP - INFERTILITY
17:00t		35+ Gyn+Obstetrics/ART- Related Conditions	35+ Gyn+Obstetrics/ART- Related Conditions
17:00	CLOSING CEREMONY of the SESSION INFERTILITY 35+		
18:00	And COMMEMORATIVE PHOTO		

Sunday, 21 September, 2025, 08:30-10:00

PLENARY SESSION	SHKHARA
Menopause and Oncological Diseases in Ob/Gyn	08:30-10:00
Chairpersons: Klaus Diedrich (DE), Elene Asanidze (GE)	

- 08:30-08:55 **Martin Birkhauser** (CH) When Should Hormone Replacement Therapy be Continued After the Age of 60 Years?
- 08:55-09:20 **Dina Kurdiani** (GE) Cervical Cancer and Pregnancy
- 09:20-09:45 **Apolon Karseladze** (RU) The Role of the Ischemia in Cervical Carcinogenesis
- 09:45-10:00 *Discussion*

SESSION – INFERTILITY 35+	TETNULDI
Oncofertility and Surgery	08:30-10:00
Chairpersons: Didem Trabulus (TR), Nino Museridze (GE)	

- 08:30-08:50 **Zaza Tsitsishvili** (GE) Early-Stage Endometrial Cancer and Reproductive Perspectives
- 08:50-09:10 **Meryem Eken** (TR) Fertility Preservation in the Context of Infertility
- 09:10-09:30 **Didem Trabulus** (TR) In Vitro Fertilization and Breast Cancer: Risk Association, Timing Strategies, and Clinical Implications
- 09:30-09:50 **Elena Mariamidze** (GE) Oncofertility in the 21st Century: Challenges and Opportunities
- 09:50-10:00 *Discussion*

SESSION – INFERTILITY 35+	MTIRALA-SHINO
Oncofertility and Surgery	08:30-10:00
Chairpersons: Tengiz Asatiani (GE), Nato Shamugia (GE)	

- 08:30-08:50 **Gian Maria Busetto** (IT) Male Fertility Preservation
- 08:50-09:10 **Irakli Kokhraidze** (GE) Breast Cancer During Pregnancy and Its Management
- 09:10-09:30 **Maka Osephaishvili** (GE) Rescue IVM of GV Oocytes: A case for Cautious Optimism
- 09:30-09:50 **Nino Chikobava** (GE) IVF and Breast Cancer: Myths and Reality
- 09:50-10:00 *Discussion*

Sunday, 21 September, 2025, 10:15-11:45

SYMPOSIUM	SHKHARA
Oncology and Reproductive Health	10:15-11:45
Chairpersons: Zion Ben Rafael (CH), Irakli Todua (GE)	

- 08:30-08:50 **Zaza Tsitsishvili** (GE) Optimal Cytoreduction – The Cornerstone of Successful Treatment of Ovarian Cancer
- 08:50-09:10 **Alfred Mueck** (DE) Breast Cancer Caused by MHT: The Two Main Mechanisms and How to Reduce the Risk
- 09:10-09:30 **Marika Japaridze** (GE) Laparoscopic Lymph-Dissection by ICG Contrast in Patients with Uterine and Cervical Cancer
- 09:30-09:50 **Nani Marsagishvili** (GE) Oncological Diseases and Recovery of Reproductive Function
- 09:50-10:00 *Discussion*

SESSION – INFERTILITY 35+	TETNULDI
Andrology and Male Fertility	10:15-11:45
Chairpersons: Nino Museridze (GE), Diego Excurra (US)	

- 10:15-10:40Giorgi Burjaliani (GE) Shockwave Therapy in Andrology:
Treatment of Erectile Dysfunction and Chronic Prostat
- 10:40-11:05Alexandre Khelaia (GE) Obstructive vs. Non-Obstructive Azoospermia:
How to Differentiate During Consultation
- 11:05-11:30George Mskhalaya (RU) Non-Obstructive Azoospermia:
When to Perform Micro-TESE and How to Prepare
- 11:30-11:45Discussion

SESSION – INFERTILITY 35+	MTIRALA-SHINO
Andrology and Male Fertility	10:15-11:45
Chairpersons: Archil Chkhotua (GE), Nato Shamugia (GE)	

- 10:15-10:40George Mskhalaya (RU) Endocrine Disorders as a Cause of Male Infertility Gian
- 10:40-11:05Maria Busetto (IT) New Methods to Evaluate DNA Fragmentation in Sperm
- 11:05-11:30Archil Chkhotua (GE) Staged Treatment of Erectile Dysfunction:
A Urologist’s Perspective
- 11:30-11:45Discussion
- 11:45-12:15Coffee break

Sunday, 21 September, 2025, 12:15-13:45

SESSION	SHKHARA
From Pubertal Endocrine Disorders to Implantation Success	12:15-13:45
Chairpersons: Gulnara Asymbekova (KG), Nino Davidova (GE)	

- 12:15-12:35Shota Janjgava (GE) Endocrine-Metabolic Panel in Pubertal Development
Disorders
- 12:35-12:55Tatiana Ermolenko (UA) Hyperprolactinemic Hypogonadism: Prediction of
Treatment Effectiveness and Management
- 12:55-13:15Manana Kochiashvili (GE) The Role of L-Arginine in Embryo Implantation and
Pregnancy Maintenance
- 13:15-13:35Nata Nakaidze (GE) Unveiling the Role of Bacteriophages in Gynecology: A
systematic Review and Case-Based Analysis
- 13:35-13:45Discussion

SESSION – INFERTILITY 35+

TETNULDI

Gyn+Obstetrics/ART-Related Conditions

12:15-13:45

Chairpersons: **Howard Carp** (IL), **Nino Museridze** (GE)

- 12:15-12:35 **Howard Carp** (IL) hCG – The Forgotten Hormone in Recurrent Pregnancy Loss
- 12:35-12:55 **Bidzina Kulumbegov** (GE) Allergy During Pregnancy: Risks, Management and Preservation
- 12:55-13:15 **Mamuka Khvedelidze** (GE) Beyond BRCA: Germline Cancer Predisposition Genes Shaping Oncofertility Strategies
- 13:15-13:35 **Ramaz Kurashvili** (GE) IVF and The Risk of Developing Gestational Diabetes Mellitus
- 13:35-13:45 *Discussion*

SESSION – INFERTILITY 35+

MTIRALA-SHINO

Gyn+Obstetrics/ART-Related Conditions

12:15-13:45

Chairpersons: **Nato Shamugia** (GE), **Suleyman Aktuna** (TR)

- 12:15-12:35 **George Tevdorashvili** (GE) The Hormonal Triangle of PCOS: From Neuroendocrine Factors to Metabolic Disorders and Infertility
- 12:35-12:55 **Nikoloz Sarauli** (GE) Innovative Surgery for Reproductive Potential: The Role of Robotic Approach in Women Over 35
- 12:55-13:15 **Maka Mantskava** (GE) Rheological Changes and Fibrinogen Levels Across Pregnancy Trimesters: Markers of Circulatory Adaptation
- 13:15-13:35 **Nia Metonidze** (GE) Gestational Diabetes: Risk Factors and Early Screening
- 13:35-13:45 *Discussion*

Sunday, 21 September, 2025, 14:00-14:30

CLOSING CEREMONY

SHKHARA

Andrea Genazzani (IT) Closing Remarks

Sunday, 21 September, 2025, 15:30-17:00

WORKSHOP-INFERTILITY 35+

WORKSHOP – INFERTILITY 35+

TETNULDI

Gyn+Obstetrics/ART-Related Conditions

15:30-17:00

Chairpersons: **Howard Carp** (IL), **Nino Museridze** (GE)

- 15:30-15:50 **Howard Carp** (IL) The Use of Anticoagulants in Recurrent Pregnancy Loss Mehmet
- 15:50-16:10 **Ali Nazli** (TR) Breast Imaging During Pregnancy and Lactation: Clinical Challenges and Current Approaches
- 16:10-16:30 **Lali Gogia** (GE) Early Pregnancy Screening for Preeclampsia Risk Factors
- 16:30-16:50 **Nani Tatishvili** (GE) Navigating Fertility with Adenomyosis: Challenges and Strategies in ART
- 16:50-17:00 *Discussion*

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Gyn+Obstetrics/ART-Related Conditions
Chairpersons: **Nato Shamugia** (GE), **George Tevdorashvili** (GE)

MTIRALA-SHINO
15:30-17:00

- 15:30-15:50

Elene Giorgadze (GE)
- 15:50-16:10

Tea Kolbaia (GE) Prenatal Diagnosis of Vasa Previa, Pregnancy Management and Prevention of Obstetric Complications
- 16:10-16:30

Tamta Motsonelidze (GE) Prenatal Diagnosis of Vasa Previa, Pregnancy Management and Prevention of Obstetric Complications
Both speakers will address the topic from different clinical perspectives
- 16:30-16:50

Ana Aivazova (GE) Silent Inhabitants: Exploring the Role of Endometrial Microbiome in Implantation Failure and ART Success
- 16:50-17:00

Discussion

Discussion Topic: Cryopreservation in Children and Adolescents
(for Those in the Audience Working in this Field)

Sunday, 21 September, 2025, 17:00-18:00

SESSION INFERTILITY 35+
Closing Ceremony and Commemorative Photo





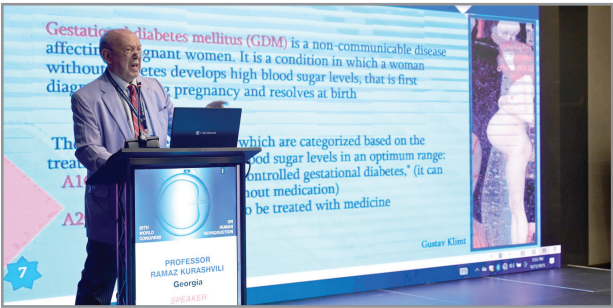














7TH INTERNATIONAL SCIENTIFIC CONFERENCE & WORKSHOP 2026
“INFERTILITY 35+”

INFERTILITY 35+

WORKSHOP



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GEORGIAN-GERMAN REPRODUCTION CENTER

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12-13 SEPTEMBER 2026
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