PREGNANCY OUTCOME AFTER TRANSFERRING GENETICALLY TESTED EMBRYOS VS. NON-TESTED EMBRYOS

***TEA CHARKVIANI**, MD;[1,2] **JENARO KRISTESASHVILI**, MD, PhD;[1] **TENGIZ ZHORZHOLADZE**, MD;[3] **NINO KUTCHUKHIDZE**, PhD;[3] **TAMAR BARBAKADZE**, MD, PhD;[2] **MARIAM GABADZE**, MD;[2] **TAMAR KBILASHVILI**, MD;[2] **MARIAM MAKHARADZE**[4]*

[1] *Faculty of Clinical and Translational Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*

[2] *Department of Reproductive Endocrinology, Georgian-American Center for Reproductive Medicine "ReproART", Tbilisi, Georgia*

[3] *Department of Embryology, Georgian-American Center for Reproductive Medicine "ReproART", Tbilisi, Georgia*

[4] *Undergraduate, David Tvildiani Medical University, Tbilisi, Georgia*

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ABSTRACT

Background: Assisted reproductive technology (ART) has transformed fertility treatment, providing opportunities for many couples who otherwise would face difficulty conceiving. A critical factor in ART success is the selection of viable embryos. Preimplantation genetic testing for aneuploidy (PGT-A) has emerged as a widely used method to improve embryo selection, enhance pregnancy outcomes, and reduce the risk of miscarriage.

Aim: To compare pregnancy outcomes between genetically tested (PGT-A) and non-tested embryos to assess the clinical value of PGT-A in optimizing ART outcomes.

Materials and Methods: A retrospective comparative study included 225 patients under 35 years of age, including recipients, patients of advanced maternal age, and those with recurrent miscarriage. All underwent ovarian stimulation with a GnRH-antagonist protocol. Blastocysts in the PGT-A group were tested using next-generation sequencing (NGS). Outcomes included biochemical pregnancy, miscarriage, and live birth.

Results: In the PGT-A group (n=110), 116 embryos were transferred. Fifty-nine pregnancies (53.6%) were achieved; 4 miscarriages (6.8%) and two biochemical pregnancies (3.4%) occurred. In total, 53 pregnancies continued to delivery (89.8% of pregnancies, 48.2% of all transfers). In the non-PGT-A group (n=115), 220 embryos were transferred, resulting in 41 pregnancies (35.7%). Of these, seven miscarried at 6 weeks (17.1%), 2 miscarried at 14–16 weeks (4.9%), and one fetus (2.4%) had a chromosomal abnormality. Thirty-two patients delivered healthy babies (78% of pregnancies, 27.8% of transfers).

Conclusion: PGT-A significantly improves pregnancy outcomes and reduces miscarriage rates by enabling the selection of euploid embryos. Its use should, however, be tailored to patient-specific factors. Larger prospective studies are needed to refine patient selection criteria.

Keywords: Preimplantation genetic testing (PGT); next-generation sequencing (NGS); in vitro fertilization (IVF); implantation rate; miscarriage rate; live birth rate; assisted reproductive technology (ART)

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Introduction

Assisted reproductive technologies (ARTs) have become a cornerstone of modern reproductive health care, offering solutions to many women and couples facing fertility challenges. As the field continues to evolve, enhancing the effectiveness of ARTs remains a priority. The success of ART treatments is influenced by various factors, including egg quality associated with the woman's age,[5–6] the protocols of controlled ovarian stimulation (COS)[7–8], the type of ovulation trigger administered for final oocyte maturation, blastocyst quality and ploidy,[9–10] endometrial condition, and overall health. Moreover, synchronization between the endometrium and embryo is critical during implantation to maximize the chances of a successful pregnancy. One significant advancement in ART is the development of preimplantation genetic testing (PGT), which has revolutionized in vitro fertilization (IVF). By enabling the identification of chromosomally normal embryos before transfer, PGT reduces the risk of implantation failure and miscarriage, thus improving pregnancy outcomes.[11]

Among the various forms of PGT, preimplantation genetic testing for aneuploidy (PGT-A) has become widely utilized to enhance embryo selection.[1] PGT-A is used to improve pregnancy outcomes and reduce the risk of miscarriage. It aims to identify embryos with the correct chromosomal complement (euploid embryos) and avoid transferring aneuploid embryos, which are more likely to result in failed implantation or miscarriage.[2] The primary goal of PGT-A is to increase implantation rates by ensuring that only euploid embryos are transferred, thereby improving the efficiency of IVF cycles.[3]

Historically, embryo selection was based solely on morphological assessment, a method that, while useful, has limitations in detecting chromosomal abnormalities that could negatively impact pregnancy viability.[12] The introduction of genetic screening techniques such as fluorescence in situ hybridization (FISH), array comparative genomic hybridization (aCGH), and next-generation sequencing (NGS) has significantly improved the accuracy of embryo assess-

ment[4]. These technologies allow for a more precise distinction between euploid, aneuploid, and mosaic embryos, thereby refining the embryo selection process.[13]

Despite the clear advantages of PGT-A in reducing implantation failure and pregnancy loss, the routine use of this technology remains a subject of debate.[14] Critics argue that PGT-A may not constantly improve cumulative live birth rates, especially in younger women with a good ovarian reserve, as some aneuploid embryos have been shown to self-correct after implantation.[15] Additionally, the cost of PGT-A adds a financial burden to an already expensive IVF process, raising questions about its cost-effectiveness.[2]

This article aims to provide a comprehensive comparison of pregnancy outcomes between genetically tested and non-tested embryos by examining key factors such as implantation rates, miscarriage rates, live birth rates, and time to pregnancy to determine the clinical value of PGT-A and its role in optimizing ART outcomes.[11]

Materials and Methods

Study Design and Participants

This retrospective study was conducted at the Georgian-American Center for Reproduction Medicine, ReproART, from January 2019 to March 2021. A total of 225 patients under the age of 35 were included. The study population also included egg donors for patients of advanced maternal age, as well as younger patients with a history of multiple miscarriages.

Inclusion and Exclusion Criteria

Patients were selected based on standardized criteria. The inclusion criteria are presented in Table 1.

Exclusion criteria included the following:

- Irregular menstrual cycles
- Abnormal body mass index (BMI)
- Polycystic ovary syndrome (PCOS)
- Sexually transmitted infections (STIs)
- Complicated obstetric history
- Endometriosis
- Uterine abnormalities
- Previous ovarian surgeries
- Male factor infertility

Ovarian Stimulation Protocol

All participants underwent ovarian stimulation using a GnRH-antagonist protocol, with prior ovarian downregulation via oral contraceptives to synchronize donor and recipient cycles. Stimulation was initiated on the fifth day after discontinuing oral contraceptives using recombinant FSH (Gonal-F, Merck Serono, Germany) in combination with highly purified human menopausal gonadotropin (hMG; Menopur, Ferring Pharmaceuticals, Switzerland).

The initial gonadotropin dose was 450 IU of FSH for the first two days, followed by dose adjustments based on ultrasound monitoring and hormonal evaluations (FSH, LH, E_2). The average stimulation duration was 11–12 days (parameters described in Table 2).

When at least one follicle reached 14 mm in diameter, Cetrotide 0.25 mg (Merck Serono, Germany) was administered. Ovulation triggering included one of the following:

- 10,000 IU hCG (Pregnyl, Organon, Netherlands)
- 1,500 IU hCG + GnRH-agonist (Decapeptyl 0.2 mg, Ferring Pharmaceuticals, Switzerland)
- GnRH-agonist alone (Decapeptyl 0.2 mg) for patients with >25 follicles

Oocyte Retrieval and Fertilization

Oocyte retrieval was performed 35 hours after ovulation trigger using transvaginal ultrasound-guided aspiration (17-gauge needles, Gynetics-Fertitech, Belgium) at 120 mmHg aspiration pressure under IV anesthesia.

All retrieved oocytes underwent intracytoplasmic sperm injection (ICSI), and fertilization assessment was conducted 16–18 hours post-ICSI.

Embryo Culture and PGT-A Testing

Embryos were cultured using Quinn's Advantage media (Origio, Netherlands). Blastocyst formation was assessed on days 5, 6, and 7 using Gardner's grading method[16]. Trophectoderm biopsy was performed for PGT-A testing at Reprogenetics/Cooper Genomics (New Jersey, USA, or UK) using next-generation sequencing (NGS).

Embryo Transfer and Endometrial Preparation

Endometrial preparation for embryo transfer involved 9 mg of estradiol daily, with additional GnRH-agonist suppression for surrogate mothers. Progesterone (Luteina 200 mg vaginally and Prolutex 25 mg intramuscularly) was initiated when endometrial thickness exceeded 8 mm.

Retrospective Analysis

A retrospective analysis was conducted to compare pregnancy outcomes between PGT-A–tested and non-tested embryos.

Analytical Approach and Statistical Methods

All statistical analyses and visualizations were performed using t-tests, ANOVA, and Python to determine the significance of differences between groups.

Results and Discussion

A total of 225 patients underwent frozen embryo transfer (FET) and were divided into two groups: the PGT-A group included 110 patients, and the non–PGT-A group included 115 patients. A total of 116 embryos were transferred in the PGT-A group; single embryos were transferred to 104 patients, and **six** patients requested the transfer of **2** blastocysts. This resulted in 59 pregnancies (53.6%), of which four pregnancies miscarried at 6 to 7 weeks of gestation (6.8%), two biochemical pregnancies occurred (3.4%), and 53 pregnancies continued to delivery (89.8% of pregnancies, 48.2% of all transfers), with live births occurring at 38 to 40 weeks of gestation.

In the non–PGT-A group, 220 embryos were transferred (1.91 embryos per patient), leading to 41 pregnancies (35.7%). Of these, seven pregnancies miscarried at 6 weeks (17.1%); 2 patients experienced late miscarriage at 14 to 16 weeks (4.9%); and one fetus out of those 2 (2.4%) was diagnosed with a chromosomal abnormality. Thirty-two patients delivered healthy babies at 37 to 40 weeks of gestation (78% of pregnancies, 27.8% of all transfers). The comparison of pregnancy outcomes is shown in Figure 1.

To rigorously test whether the difference in pregnancy rates between the PGT-A and non–PGT-A groups was statistically significant, a logistic regression analysis (Figure 2) was performed. The results revealed a statistically significant difference between the PGT-A and non–PGT-A groups ($P < 0.001$). The Z value (−2.18) confirmed the distinct outcomes in the PGT-A group after adjusting for group size. The ROC curve demonstrated the model's strong predictive accuracy, with an AUC of 0.90, highlighting its effectiveness in distinguishing between the two groups regarding pregnancy outcomes.

The findings of this study support the efficacy of PGT-A in improving pregnancy outcomes by increasing implantation rates, reducing miscarriage rates, and optimizing embryo selection. The pregnancy rate in the PGT-A group (53.6%) was significantly higher than in the non–PGT-A group (35.7%), demonstrating the advantage of selecting euploid embryos. Furthermore, the miscarriage rate was lower in the PGT-A group (6.8%) compared with the non–PGT-A group (17.1%), emphasizing the role of genetic testing in reducing early pregnancy losses.

Numerous studies have compared the efficacy of PGT-A with non–PGT-A embryo transfers, with mixed results depending on the patient population and study design. PGT-A is consistently associated with higher implantation and clinical pregnancy rates, particularly in older women and those with recurrent pregnancy loss. For instance, clinical pregnancy rates after PGT-A have been reported to reach approximately 60%, significantly higher than non–PGT-A transfers.[17] Similarly, Scott et al demonstrated that PGT-A cycles resulted in an implantation rate of approximately 65%, further highlighting the technique's potential to improve pregnancy outcomes in select populations.

One of the key advantages of PGT-A is its ability to reduce miscarriage rates by selecting euploid embryos, which have a lower likelihood of resulting in early pregnancy loss. Studies such as Dahdouh et al found that miscarriage rates after PGT-A were significantly lower, often below 10%, compared with non–PGT-A transfers.[18]

However, despite these advantages, the universal application of PGT-A remains controversial. Some studies, such as Mastenbroek et al, found no significant difference in live birth rates between PGT-A and non–PGT-A groups in younger women, raising concerns about the necessity of genetic testing in patients with a good prognosis.[19] These findings suggest that PGT-A should be applied selectively rather than routinely, particularly in younger patients with high-quality embryos.

In addition to these clinical considerations, the cost-effectiveness of PGT-A has become an essential factor in evaluating its broader application in IVF treatments. While the total cost of an IVF cycle that includes PGT-A is higher than that of a conventional IVF cycle without genetic testing, the cost-effectiveness of PGT-A becomes evident when considering long-term outcomes. Transferring non–PGT-A embryos is associated with lower implantation rates, higher miscarriage risks, and increased emotional and financial burdens on patients.[20]

Patients undergoing IVF without genetic testing may require multiple embryo transfers because of failed implantations, ultimately leading to increased expenses over time. Studies have shown that for specific age groups, PGT-A can reduce the average cost per infant, making it a cost-effective strategy in particular populations.[21]

Failed implantation and miscarriage result in psychological distress and emotional strain, prolonging the journey to parenthood. Research indicates that infertility and repeated IVF failures can lead to increased rates of depression and anxiety among patients.[22] The physical and psychological stress of repeated miscarriages can also place couples at risk of relationship strain.

Recurrent pregnancy loss has been associated with significant psychological distress for both partners, potentially leading to symptoms of depression, anxiety, and lowered self-esteem. Additionally, the emotional toll of recurrent miscarriages can negatively impact couples' relationships and sexual intimacy.[23]

In cases where a non–PGT-A embryo results in pregnancy but later leads to miscarriage, medical interventions such as dilation and curettage (D&C) may be necessary, which can pose risks to the patient's reproductive health and reduce future pregnancy success rates. For instance, a study published in *Human Reproduction* found that a history of curettage is associated with an increased risk of preterm birth in subsequent pregnancies. However, other research indicates that D&C does not significantly affect future pregnancy outcomes.[24]

Overall, this study supports the use of PGT-A as an effective tool for improving pregnancy outcomes, particularly in women at risk of implantation failure or miscarriage. However, its clinical application should be tailored based on individual patient characteristics, ovarian reserve, and clinical history to maximize the chances of a successful pregnancy. Further large-scale studies are needed to refine the indications for PGT-A and confirm its long-term benefits in diverse patient populations.

Understanding these differences is crucial for both reproductive specialists and patients in making informed decisions regarding the use of genetic testing in IVF cycles.[13]

Conclusion

PGT-A offers a significant advantage in improving pregnancy outcomes by selecting euploid embryos and reducing miscarriage rates. However, its routine use should be individualized and tailored to patient-specific factors. Further large-scale studies are needed to optimize patient selection criteria for PGT-A, ensuring its application is both cost-effective and beneficial for intended parents.

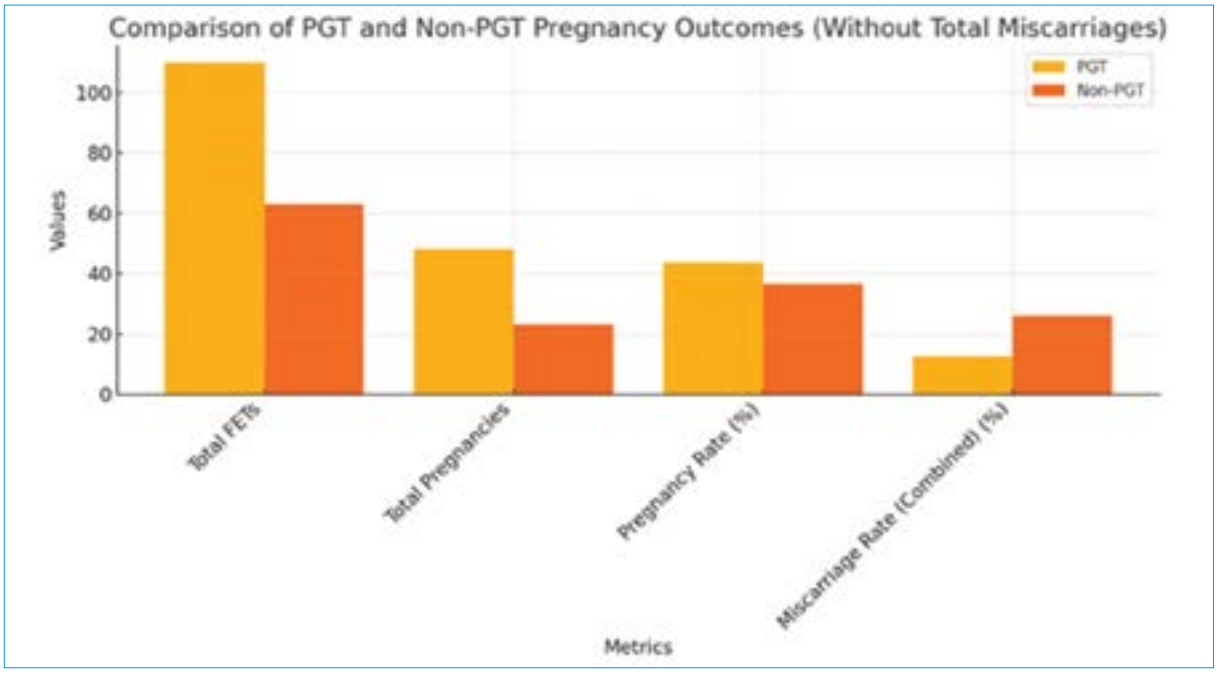

Figure 1. Graphical comparison of pregnancy outcomes following transfer of genetically tested (PGT-A) and non-tested embryos. Pregnancy rates were higher and miscarriage rates were lower in the PGT-A group.

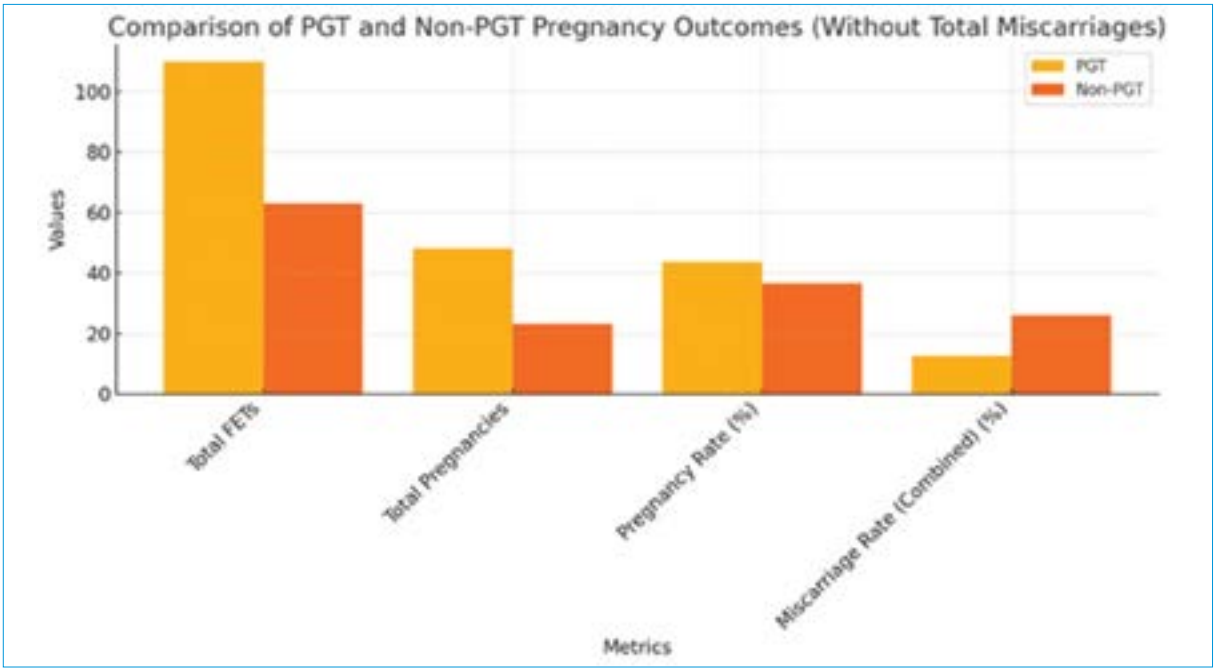

Figure 2. Receiver operating characteristic (ROC) curve analysis comparing pregnancy outcomes between genetically tested (PGT-A) and non-tested embryo transfers. Logistic regression analysis revealed a statistically significant difference between the two groups, with an area under the curve (AUC) of 0.90, indicating strong predictive accuracy for distinguishing pregnancy outcomes based on embryo genetic testing.

Table 1. Patient Inclusion Criteria and Average Indicators

Parameter	Average Value
Age	25.0 – 35 years
AMH (ng/mL)	4.2 ± 2.0
Antral Follicle Count (AFC)	24.7 ± 7.6
BMI	21.9 ± 2.4
Follicle-Stimulating Hormone (FSH) (mIU/mL)	7.8 ± 2.1
Thyroid-Stimulating Hormone (TSH) (mIU/mL)	2.2 ± 1.3
Prolactin (PRL) (ng/mL)	16.3 ± 5.7
Sperm Parameters	Normal

Table 2. Ovarian Stimulation Parameters

Parameter	Mean Value ± SD
FSH Level at Downregulation (mIU/mL)	3a.6 ± 2.5
Estradiol (E2) Level at Downregulation (pg/mL)	10.4 ± 8.6
Total Gonadotropins Administered (IU)	3203 ± 536
Stimulation Duration (Days)	10.5 ± 2.1
E2 Level on Trigger Day (pg/mL)	7325 ± 1567
Follicle Diameter at Retrieval (mm)	18.4 ± 1.7
Total Retrieved Oocytes	± 5.5

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