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Forty and Beyond: A SWOT Analysis of PGT-A in the Context of Aging and Fertility

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Abstract

Preimplantation genetic testing for aneuploidy (PGT-A) is widely used in in vitro fertilization (IVF) to detect chromosomal abnormalities in embryos. This testing employs various platforms—including quantitative PCR, array comparative genomic hybridization (aCGH), and next-generation sequencing (NGS)—each with its own advantages and limitations. The goal of these technologies is to enhance clinical outcomes, reduce the time to pregnancy, and ultimately improve the likelihood of delivering a healthy baby. Additionally, emerging approaches such as non-invasive PGT using spent culture medium show promise for future applications. However, it is important to recognize that PGT-A functions as a screening tool rather than a definitive indicator of the chromosomal status of embryos or fetuses. While advocates claim that PGT-A enhances IVF outcomes, critics argue that it lacks adequate clinical validation and may reduce live birth rates due to its high false-positive rate. This article employs a SWOT analysis to evaluate the advantages, challenges, opportunities, and risks of PGT-A in women of advanced maternal age.

Keywords: PGT-A, SWOT, Strength, Weakness, Opportunity.

Introduction

Preimplantation genetic testing for aneuploidy (PGT-A) is widely used in in vitro fertilization (IVF) to detect chromosomal abnormalities in embryos. This testing employs various platforms—including quantitative PCR, array comparative genomic hybridization (aCGH), and next-generation sequencing (NGS)—each with its own advantages and limitations (1, 2). The goal of these technologies is to enhance clinical outcomes, reduce the time to pregnancy, and ultimately improve the likelihood of delivering a healthy baby. Additionally, emerging approaches such as non-invasive PGT using spent culture medium show promise for future applications (1).

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However, it is important to recognize that PGT-A functions as a screening tool rather than a definitive indicator of the chromosomal status of embryos or fetuses (3). While advocates claim that PGT-A enhances IVF outcomes, critics argue that it lacks adequate clinical validation and may reduce live birth rates due to its high false-positive rate (4).

The primary aim of PGT-A is to identify embryos with the highest potential for successful implantation, particularly benefiting women with advanced maternal age (AMA), recurrent pregnancy loss (RPL), or repeated implantation failure (RIF) (5). Its utilization in IVF cycles across the United States has been steadily increasing. National data from the Society for Assisted Reproductive Technology (SART) indicate that the proportion of IVF cycles employing PGT rose from 14% in 2014 to 44% in 2019 (6, 7).

In favorable prognosis patients, some studies have reported improved outcomes with PGT-A (8, 9), while others have not demonstrated clear benefits (5, 10, 11). A systematic review from the Cochrane Database found that there was insufficient high-quality evidence to indicate differences in cumulative live-birth rate (CLBR), live-birth rate (LBR) following the first embryo transfer, or miscarriage rate between cycles performed with and without PGT-A (12). Conversely, for women with advanced maternal age, the situation differs somewhat; a post hoc analysis of the STAR trial revealed an increased ongoing pregnancy rate (OPR) per embryo transfer in patients aged 35–40 years (5).

A randomized controlled trial involving women aged 38–41 years compared two approaches: routine blastocyst transfer and a PGT-A strategy that included a single blastomere biopsy on day 3 with transfer on day 5 (13). Although clinical pregnancy rates were similar between the groups, the PGT-A group exhibited a significantly lower miscarriage rate (2.7% vs. 39%, P=0.0007) and, consequently, a higher live birth rate (52.9% vs. 24.2%, P=0.0002). Retrospective studies have further suggested that PGT-A may improve live birth rates per cycle in women aged 38–40 years (14) and enhance implantation rates in women aged 40–43 years, with euploid embryos achieving implantation rates of 50.9% compared to 23.8% and 25.4% in unscreened fresh and frozen-thawed embryo transfer cycles, respectively (15, 16). Moreover, an observational prospective cohort study from a single center, involving patients aged 38–44 years, demonstrated that PGT-A was associated with a higher per-transfer live birth rate and lower rates of multiple pregnancies and miscarriages relative to controls (17). Despite these findings, some experts argue that the overall benefits of PGT-A remain uncertain and may depend on factors such as maternal age and the specific outcome measures reported—whether clinical pregnancy, live birth, miscarriage, or cumulative rates (5, 18–20). Ethical concerns have also been raised regarding the potential reduction in cumulative pregnancy rates due to the discarding of embryos (21). In women over 40, who typically experience declines in both oocyte quality and quantity, PGT-A may help in selecting the most viable embryo for transfer (22).

SWOT analysis (Strengths-Weaknesses-Opportunities-Threats) is a framework originally developed for business, providing organizations with a structured approach to evaluate their internal operations and external environment. Rooted in the principles of business strategy, it offers a systematic method to understand an organization's unique position within its competitive landscape (23) and has been adapted for use in health sciences (24). By focusing on internal strengths and weaknesses, SWOT analysis helps identify external threats and opportunities, thereby addressing gaps that could hinder the broader application of a method or system. This article employs a SWOT analysis to evaluate the advantages, challenges, opportunities, and risks of PGT-A in women of advanced maternal age.

1-Strengths

1.1 Improved pregnancy rates

PGT-A has demonstrated the ability to enhance clinical and ongoing pregnancy rates in women of advanced maternal age by enabling the selection of euploid embryos for transfer (5, 25).

1.2 Reduced miscarriage rates

PGT-A can reduce miscarriage rates by detecting aneuploid embryos, which are more frequently observed in older women (26, 27). Data from the Latin American registry indicate that, in women aged 40 and older, the miscarriage rate decreased from 21.9% to 13.9% (P<0.001), while the live birth rate increased from 19.5% to 35.9% with the application of PGT-A (28).

1.3 Increased live birth rates

PGT-A has been shown to improve live birth rates (LBR) in women over 40 by enabling the selection of euploid embryos for transfer (13–16, 29, 30). In a

study by Lee et al., women aged 40–43 years who underwent frozen embryo transfer (FET) of euploid embryos demonstrated significantly higher implantation rates and LBR per transferred embryo compared to unscreened embryos in both fresh and FET cycles (16). Collectively, these findings suggest that PGT-A may offer particular benefits for patients of advanced maternal age, especially those with a sufficient ovarian reserve (31).

1.4 Improved embryo selection and reproductive outcome per transfer

Multiple studies have demonstrated that PGT-A significantly improves live birth rates in women aged 40 and older (30, 37). Aneuploidy screening for embryo selection markedly enhances implantation success and reduces miscarriage rates (27). Additionally, PGT-A lowers the abortion rate in women aged 41–42 (38). In one study by Lee et al., women aged 40–43 who underwent frozen embryo transfers of euploid embryos achieved significantly higher implantation rates and live birth rates per transferred embryo compared to those receiving unscreened embryos in both fresh and frozen cycles (16).

A post hoc analysis of the Single Embryo Transfer of Euploid Embryo (STAR) trial demonstrated that next-generation sequencing (NGS) improves ongoing pregnancy rates in women aged 35 years and older, with increased ongoing pregnancy rates per embryo transfer observed in patients aged 35–40 years (5). Additionally, data from 8,175 single embryo transfers following PGT-A and embryo cryopreservation indicate that selecting euploid embryos can mitigate the age-related decline in reproductive efficiency (39). Moreover, information from the Latin American registry revealed that in women aged 40 and above, the miscarriage rate decreased from 21.9% to 13.9% ($P<0.001$) while the live birth rate increased from 19.5% to 35.9% with the use of PGT-A (28).

One RCT focused on women with advanced maternal age (38–41 years) and randomized participants before the cycle start to either routine blastocyst transfer or a PGT-A protocol, which involved a single blastomere biopsy on day 3 with transfer on day 5. The study found that the live birth rate was significantly higher in the PGT-A group, both per transfer (52.9% vs. 24.2%, $P=0.0002$) and per cycle (36% vs. 21.9%, $P=0.031$) (13). Additionally, retrospective studies have suggested that PGT-A improves live birth rates per cycle in women aged 38–40 years (14) and enhances implantation rates in women aged 40–43 years, with euploid embryos achieving an implantation rate of 50.9% compared to 23.8% in unscreened fresh cycles and 25.4% in frozen embryo transfer cycles (16). Moreover, an observational prospective cohort study involving patients aged 38–44 years at a single center demonstrated that PGT-A is associated with higher live birth rates and lower rates of multiple pregnancies and miscarriages, without adversely affecting cumulative delivery rates or neonatal outcomes (17).

1.5 No determinantal effect on CLBR

The miscarriage rate was significantly lower in the PGT-A group. Recent studies suggest that implementing PGT-A in women with advanced maternal age does not negatively affect the cumulative live birth rate (CLBR) per oocyte retrieval and may even improve it (40, 41). Moreover, PGT-A substantially reduces the risk of implantation failure and spontaneous abortion due to fetal aneuploidies, making it a valuable tool for embryo selection (40, 41). In a subgroup analysis of freeze-all cycles, miscarriage rates were markedly reduced in women aged 35–40 (42). However, PGT-A appears less effective in women aged 42 and older with a low antral follicle count (AFC ≤8) (40). Therefore, comprehensive counseling is recommended for women over 43 due to their significantly lower chances of success and higher risk of embryo aneuploidies. Supporting this, Ubaldi et al. (43) found that among women over 44 with a good ovarian reserve, only 14.0% of embryos were euploid; no euploid blastocyst was detected in patients older than 46, while the rates were 14.4% for those aged 44.0–44.9 and 4.5% for those aged 45.0–45.9. Notably, the delivery rate per transfer was 57.1%.

In patients aged 44.0–44.9 years, the delivery rate per cycle was 10.6%, compared to only 2.6% in those aged 45.0–45.9 years. In a multicenter randomized trial by Rubio and colleagues involving women aged 38–41 years, who underwent day-3 embryo biopsies with array CGH, the delivery rate following the initial transfer was significantly higher in the PGD-A group both per transfer (52.9% vs. 24.2%) and per patient (36.0% vs. 21.9%), although cumulative live birth rates were comparable. Additionally, PGT-A substantially reduced miscarriage rates (2.7% vs. 39.0%) and shortened the time to pregnancy (7.7 weeks vs. 14.9 weeks) (13). Considering these factors, ensuring procedural safety and minimizing time to pregnancy are critical. Patients should be counseled that with increasing age, the likelihood of producing only aneuploid embryos rises, making the attainment of

a euploid blastocyst more challenging. This challenge is compounded by factors such as poor follicular development, unsuccessful oocyte retrieval, and reduced blastocyst formation rates, all of which can lead to cycle cancellation. Improved embryo selection in women with advanced maternal age and enhanced implantation per transfer could reduce the number of transfers needed to achieve implantation per oocyte retrieval.

2-Weaknesses

2.1 The lack of high quality evidence in improving IVF outcomes

Several studies have reported a lack of benefit from PGT-A. For instance, Henderson et al.'s RCT using FISH provided evidence against employing PGT in advanced maternal age (AMA) patients undergoing IVF (47). Similarly, Staessen et al. (2004) found that PGT-A, as assessed by FISH, did not improve clinical outcomes per initiated cycle in AMA patients when there were no restrictions on the number of embryos transferred (48). Moreover, Mastenbroek et al. (2007) reported that preimplantation genetic screening with FISH not only failed to increase, but actually significantly reduced, ongoing pregnancy and live birth rates in women of advanced maternal age (49). In short, early versions of PGS (PGS 1.0) were unsuccessful—a meta-analysis of 11 randomized controlled trials even indicated that it might be detrimental for older women (50).

Further evidence suggests that PGT-A yields unfavorable outcomes in women aged ≥42 years with an antral follicle count (AFC) ≤8, leading to poor live birth outcomes (40). Specifically, when a woman is aged ≥42 years or has an AFC ≤8, the expected live birth outcome following PGT-A is diminished (40). Ubaldi et al. (43) assessed PGT-A in women over 44 with a good ovarian reserve and found that only 14.0% of embryos were euploid. Notably, no euploid blastocysts were detected in patients older than 46, while the euploid rates for patients aged 44.0–44.9 and 45.0–45.9 were 14.4% and 4.5%, respectively. Although the delivery rate per transfer was 57.1%, the delivery rate per cycle was only 10.6% for those aged 44.0–44.9 years and a mere 2.6% for patients aged 45.0–45.9 years.

2.2 Limited number and inconsistent non-standardized RCT studies

Success rates in assisted reproductive technology can be reported in various ways—such as intention-to-treat, per patient, per cycle, and per transfer (both fresh and frozen)—which complicates the comparison of outcomes across studies. Moreover, certain metrics, like implantation rates and success per transfer, may not be appropriate; thus, pregnancy rates should ideally be calculated using cycles initiated rather than embryo transfers as the denominator (51). Only a limited number of randomized controlled trials (RCTs) have been published (8, 9, 52), and each has faced criticism for issues such as small patient groups or including only patients who underwent a transfer (8), flawed study design (52), or restriction to younger patient populations (9). Notably, there are no well-designed RCTs available for populations with advanced maternal age (AMA), recurrent implantation failure (RIF), or recurrent miscarriages (RM) (51, 53). Furthermore, many studies have predominantly involved patients with unfavorable prognoses, resulting in a limited number of low-quality embryos (54–56).

2.3 Cost: PGT-A can be expensive, adding to the overall cost of IVF treatment

PGT-A is an expensive procedure, and its cost may be a barrier for some women (44). However, quantifying the true cost is challenging, as it should encompass not only the expenses of the IVF cycle, molecular techniques, and genetic and psychological counseling, but also the costs associated with managing miscarriages and multiple pregnancies. One study reported that, for women of advanced maternal age, IVF alone was less costly per healthy infant compared to IVF with PGT-A (57), whereas another study found that, for fresh IVF cycles in women over 37 with at least one blastocyst, incorporating PGT-A was a cost-effective strategy in terms of achieving one live birth (58). Further research is needed to fully assess the economic impact of PGT-A, considering its potential to reduce overall costs (59).

2.4 Technical challenges

PGT-A requires a high level of technical expertise, and its results may not always be entirely accurate (44, 46). The first generation of Preimplantation Genetic Screening, known as PGS 1.0, was used in IVF to screen embryos for chromosomal abnormalities. The primary technology employed for PGS 1.0 was array comparative genomic hybridization (aCGH), which analyzed DNA from a single cell biopsied from a day 3 embryo to detect gains or losses of chromosomal material. This approach examined all 24 chromosomes (22 autosomes and 2 sex chromosomes) to identify aneuploidies. However, PGS 1.0 had limited resolution, potentially missing smaller chromosomal

abnormalities such as deletions or duplications, and the day 3 biopsy might not have been representative of the entire embryo. The technique has since evolved into PGS 2.0, also known as next-generation sequencing (NGS), which offers higher resolution, improved accuracy, and the ability to detect smaller chromosomal alterations.

2.5 Limited accuracy:

PGT-A is not infallible and carries inherent risks of false positive and false negative results (45). As a screening test, PGT-A can occasionally misclassify embryos: a false positive occurs when an embryo that is actually euploid is incorrectly labeled as aneuploid, whereas a false negative happens when an embryo that is truly aneuploid is mistakenly classified as euploid. Estimating the rates of these errors is challenging. In clinical practice, if an embryo presumed to be euploid fails to result in a pregnancy, it is impossible to retrospectively verify its chromosomal status, obscuring the true false negative rate. Conversely, most embryos labeled as aneuploid are discarded, so their potential to yield a healthy pregnancy remains unknown.

False positive diagnoses in PGT-A arise from several factors. First, an earlier erroneous belief regarded mosaic embryos as abnormal, leading to their exclusion from transfer. Second, technical issues—particularly in less experienced centers—can result in over-diagnosis of mosaicism (technical mosaicism) (60). Third, older platforms such as aCGH have a tendency to misclassify both euploid and mosaic embryos as aneuploid. Until recently, mosaic embryos were routinely treated as abnormal (i.e., as false positives), resulting in their cryopreservation or disposal (61), despite evidence that mosaic embryos can lead to live births (62–64). Discarding these embryos can reduce both the pregnancy rate (PR) and live birth rate (LBR) (62, 65). Moreover, a higher technical error rate increases the likelihood that euploid embryos will be incorrectly diagnosed as mosaic and consequently discarded. In contrast, modern PGT-A methods employing next-generation sequencing (NGS) exhibit low error rates (0–2%), with positive and negative predictive values around 4% (34, 36, 66–69). On the other hand, older techniques, particularly aCGH, have higher false negative rates, sometimes misclassifying aneuploid embryos as euploid, which may then be transferred only to result in miscarriage. Subsequent chromosomal reassessment of products of conception (POC) using NGS has confirmed that these embryos were indeed aneuploid (70).

The predictive value of an abnormal result may only be resolved by performing a non-selection study. In such studies, blastocysts are biopsied and transferred prior to performing any analysis. Selection of blastocysts for transfer is based merely on morphology. Once the outcome from the cycle is known, the sample is analyzed, and it is determined if the analysis correctly predicted the clinical outcomes. In the non-selection study of Tiegs et al., 2021 (71), a total of 402 patients underwent 484 single, frozen blastocyst transfers. All embryos were biopsied, and the biopsy results were blinded till the outcome was known. A significant difference in outcomes by PGT-A diagnosis was observed: embryos diagnosed as euploid had a chemical pregnancy rate, clinical pregnancy rate, and sustained implantation or delivery rate of 82.1%, 73.3%, and 64.7%, respectively, while embryos diagnosed as aneuploid had a chemical pregnancy rate, clinical pregnancy rate, and sustained implantation or delivery rate of 40.2%, 23.5%, and 0%, respectively.

Although the aneuploid clinical error rate was 0% in the above study, the true error rate is unlikely to be 0%, given the numerous possibilities for the introduction of error throughout the process of aneuploidy screening. Such potential sources of error include sampling error (i.e., the screening of trophoectoderm [TE] cells rather than the inner cell mass [ICM] or whole embryo), de novo postzygotic mitotic errors and embryonic mosaicism, DNA amplification failure, contamination, spontaneous conception, and inadvertent mix-up of DNA samples (72-74). Therefore, although unlikely to truly be zero in a much larger sample, the aneuploid call clinical error rate for this PGT-A assay lies between 0% and 2.43%, which is exceedingly low (61, 67, 75).

2.6 Managing mosaicisms:

PGT-A classifies embryos into several categories:

- **Euploid:** All cells contain a normal complement of chromosomes.
- **Aneuploid:** All cells contain an abnormal number of chromosomes.
- **Segmental Aneuploid:** Every cell has a duplication or deletion affecting a portion of a chromosome.
- **Mosaic:** The embryo contains a mix of euploid and aneuploid cells.
- **Segmental Mosaic:** Some cells are euploid while others display segmental aneuploidy.

- **Inconclusive:** DNA amplification or analysis has failed.

Embryonic mosaicism results from mitotic errors occurring after fertilization—such as mitotic non-disjunction, anaphase lag, or chromosome deletion/duplication. The ratio of aneuploid to euploid cells in an embryo depends on the timing of the error during cleavage. For example, an error early in mitotic division may lead to high-level mosaicism (a greater proportion of aneuploid cells), whereas a later error typically results in low-level mosaicism (a lower proportion of aneuploid cells) (76).

However, ART is not considered a risk factor for mosaicism (77–79). It is important to distinguish between true biological mosaicism and technical mosaicism. Prenatal testing has shown that the prevalence of genuine biological mosaicism is less than 0.3% (80). The substantial reduction in mosaicism observed from pre- to post-implantation stages is thought to result from the selective elimination of aneuploid cells—either through the competitive growth advantage of euploid cells or via apoptosis of abnormal cells (81, 82).

If a clinic experiences a mosaicism rate exceeding 5%, it is advisable to examine both embryological practices and PGT-A protocols to identify potential causes for this unacceptably high level of technical mosaicism (78). Potential sources of technical mosaicism include DNA amplification artifacts due to incomplete cell lysis, contamination, suboptimal sample handling or transport, poor biopsy technique, excessive laser use, compromised biopsy cell quality, and the selection of algorithms used for normalizing chromosome mapping bins (60).

The transfer of mosaic embryos is increasingly considered a viable option for patients who do not have euploid embryos available. To date, over 2,700 mosaic embryo transfers have been documented (83). Several retrospective studies have reported that transferring mosaic embryos is associated with acceptable, albeit reduced, rates of embryo implantation and sustained pregnancy, as well as increased miscarriage rates compared with transfers of euploid embryos (26, 45, 63, 64, 70, 84-86). However, these retrospective findings are influenced by significant selection bias. Mosaic embryos are typically transferred only as a last resort, meaning that their reproductive performance is often assessed in a highly selected group of patients who have already experienced failed implantations with euploid embryos. Additionally, mosaic embryos are sometimes transferred in cases where only aneuploid embryos are available, further biasing outcomes toward a poor-prognosis population.

Conversely, a prospective non-selection study found that mosaicism levels below 50% do not adversely affect early embryonic development, with ongoing pregnancy and miscarriage rates comparable to those of euploid embryos (87). Notably, fewer than 1% of transferred mosaic embryos resulted in an ongoing aneuploid pregnancy consistent with the original PGT-A findings (83). This may be due to the abnormal cells either undergoing apoptosis or proliferating more slowly than their normal counterparts. Additionally, it is important to recognize that some mosaic diagnoses may be technical artifacts, and true self-correction via mechanisms such as uniparental disomy is exceedingly rare (88, 89).

2.7 Concordance between trophectoderm biopsy (TEB) and inner cell mass (ICM).

TEB consists of a sample of 3 to 10 blastomeres from the trophectoderm—the tissue that will form the placenta—whereas the embryo itself develops from the inner cell mass (ICM). Concerns have been raised about whether a small TE sample can accurately represent the ICM, leading to questions about their concordance (90–94). It is important to note that earlier studies reporting discordance often used outdated platforms and suffered from methodological issues that may have inflated discordance rates between TEB and the ICM (92).

In a robust concordance study, Capalbo et al. (2020) (87) evaluated 73 unselected human blastocysts donated for research. The ICM was isolated, and the trophectoderm was divided into four biopsies. All five samples—four from the trophectoderm and one from the ICM—were analyzed using blinded next-generation sequencing (NGS). The findings showed that when the index TEB was classified as euploid, low mosaic, or medium mosaic, the ICM was euploid in 99.6%, 99.3%, and 95.5% of cases, respectively. Furthermore, if the index TEB was aneuploid, the ICM was aneuploid in 98% of cases. Overall, the study demonstrated a very high concordance between the TEB and the ICM. Mosaicism detected in the trophectoderm generally did not reflect in the ICM—embryos with euploid, low mosaic, or medium mosaic TEB results were mostly euploid in the ICM, while aneuploid TEB results corresponded with aneuploid ICM findings. However, in cases where the TEB exhibited high mosaicism, the ICM was aneuploid in only 65% of instances.

2.8 Invasiveness of the procedure

Scott et al. (2013) reported a significant 39% reduction in implantation rate when a cleavage-stage biopsy was performed compared to controls. This reduction is likely due to the inherent fragility of embryos at this early stage, before embryonic genome activation has occurred, meaning that the removal of even a single cell—which can represent 12.5–16.6% of the total blastomeres—can compromise subsequent developmental processes. This detrimental effect is also evidenced by a lower rate of blastocyst formation following cleavage-stage biopsy compared to undisturbed embryos (47, 96, 97).

As a result, blastocyst biopsy is increasingly replacing cleavage-stage biopsy. The advantage of trophectoderm biopsy (TEB) lies in its greater technical and biological robustness, leading to fewer technical errors and a reduced impact of mosaicism on molecular analysis. However, the success of this strategy depends on proper blastocyst culture and vitrification techniques. When performed by experienced practitioners, blastocyst biopsy does not compromise embryo viability or implantation potential, as demonstrated by well-designed non-selection studies (67, 71). One reason for this is that only 5 to 6 trophectoderm cells are removed from a blastocyst, which typically contains around 200 cells, and these cells are taken from a part of the blastocyst that is less critical to embryonic development.

It should be noted that blastocyst biopsy can negatively affect an embryo's implantation potential when performed by less experienced personnel, which likely accounts for significant inter-center variability in PGT-A outcomes (75, 98). When the risk of biopsy-induced damage is high and leads to substantial embryo loss, PGT-A only enhances embryo selection if the underlying aneuploidy rate exceeds a specific threshold. Conversely, if technical embryo loss remains low (<10%), PGT-A can improve selection even in younger patients with aneuploidy rates around 20%. However, if embryo loss rates are high (30% or more), the benefit is only evident in cases with aneuploidy rates of 60% or higher, as is typically seen in women over 35.

In parallel, less invasive techniques for blastocyst biopsy are under development, utilizing cell-free DNA obtained from blastocoel fluid or blastocyst-spent culture media. Nonetheless, there is currently no consensus regarding the concordance of these methods with the true genetic status of the embryo. Limitations of non-invasive PGT-A include incomplete representation of the entire embryonic genome, potential contamination with maternal DNA, and compromised nucleic acid integrity. Owing to these limitations, the clinical value of non-invasive PGT-A remains a subject of debate (99).

3- Opportunities

3.1 Rising demand

Data from the Latin American registry indicate that in women aged ≥40 years, nearly 77% of 10,183 embryos were aneuploid, and PGT-A currently represents the primary tool available to address this high rate of aneuploidy (28).

3.2 Adoption of elective single embryo transfer (eSET)

Multiple pregnancies are a recognized complication of ART and are linked to adverse outcomes such as preterm birth, NICU admissions, and perinatal death (100). To mitigate the risk of multiple pregnancies, it is recommended to reduce the number of embryos transferred (101). Elective single embryo transfer (eSET) is considered the most practical strategy to avoid multiple pregnancies following IVF cycles. Additionally, the use of PGT-A allows for the selection of euploid embryos for transfer (102). A Cochrane review found no significant difference in cumulative live birth rates (CLBR) between a single cycle of double embryo transfer and repeated eSETs (103). Therefore, employing eSET alongside PGT-A for selecting euploid blastocysts in patients with advanced maternal age could be an effective approach (104).

3.3 Reduction in Time to Pregnancy

Pregnancy after the age of 35 is often seen as a race against time, where repeated ART failures or miscarriages can impose significant financial and psychological burdens. By employing PGT-A to transfer only euploid embryos, couples may achieve conception more rapidly—a considerable advantage for patients of advanced maternal age. For example, Rubio et al. (13) demonstrated that the time to a successful pregnancy was reduced in patients undergoing PGT-A, and another retrospective cohort study of AMA women similarly showed that the PGT-A group reached a clinical pregnancy resulting in a live birth in a shorter timeframe (105).

3.4 Advancements in technology

Advancements in technology, such as next-generation sequencing (NGS), have significantly increased the accuracy and efficiency of PGT-A. Initially, PGT-A was performed using fluorescent in situ hybridization (FISH) with seven to nine probes targeting the most commonly abnormal chromosomes on one to two interphase blastomeres from a cleavage-stage embryo (32). Since then, a variety of advanced methods have been introduced, including array comparative genomic hybridization (aCGH), single-nucleotide polymorphism (SNP) arrays, quantitative PCR (qPCR), and NGS. These techniques differ in their abilities to detect ploidy status, mosaicism, and translocations, each with its own set of advantages and limitations. For example, SNP arrays can reliably detect mosaic changes—provided there is an adequate number of trophectoderm cells—and can efficiently identify unbalanced translocations, partial aneuploidies, and uniparental disomies (33). In contrast, methods such as qPCR, which do not employ whole genome amplification (WGA), can rapidly identify aneuploidies but offer lower genomic coverage and are less effective at detecting small deletions, duplications, structural chromosomal aberrations, or mosaicism (34). NGS currently represents the most advanced method for PGT-A, as it reduces DNA sequencing costs while enhancing the detection of unbalanced translocations, partial aneuploidies, and mosaicism (35, 36).

4-Threats

4.1 Controversy: The use of PGT-A remains contentious, with some critics arguing that it may result in the unnecessary discarding of embryos that could be viable (106).

4.2 Regulatory Challenges: PGT-A faces significant regulatory hurdles, particularly in countries with stringent laws governing fertility treatments (107).

4.3 Patient Expectations: The application of PGT-A can lead to unrealistic expectations among patients, especially if the results are not communicated accurately (108).

4.4 Emergence of New Technologies: Innovations such as non-invasive prenatal testing (NIPT) have the potential to eventually replace PGT-A (109).

4.5 Market Threats: Declining birth rates and the increased use of alternative fertility treatments may reduce demand for PGT-A, adversely affecting the industry (110).

4.6 Economic Threats: Changes in reimbursement policies or insurance coverage could limit access to PGT-A (111).

4.7 Ethical Threats: Ethical concerns surrounding PGT-A might lead to decreased public acceptance of the procedure (112).

4.8 Emotional and Psychological Impact: The psychological burden associated with PGT-A is a major factor contributing to treatment discontinuation (113).

4.9 Adverse Obstetrical, Neonatal, and Long-Term Outcomes: Infertility is linked to obstetrical complications, perinatal adversities, and less optimal neurological development, which may put children conceived with PGT-A at a higher risk for adverse outcomes compared to those conceived through PGD (114). Moreover, concerns have been raised about the potential impact of the invasive embryo biopsy on child development. Although data on the long-term developmental and health outcomes of children born after PGT-A are limited, current studies have not found statistically significant differences in mental, psychomotor, neurological, or behavioral outcomes when compared with children conceived without PGT-A (49, 115-120

Table 1: Strengths, weaknesses, opportunities, and threats analysis of PGT-A for women with advanced maternal age.

Strengths	Weaknesses
- **Improved embryo selection and reproductive outcome per transfer** - **Improved pregnancy rates** in women over 40 - **Reduced miscarriage rates:** by identifying aneuploid embryos, which are more common in older women - **Increased live birth rates** in women over 40 - **No determinantal effect on CLBR**	- **The lack of strong evidence in improving IVF outcomes** - **Limited number and inconsistent non-standardized RCT studies** - **Cost barrier** - **Technical challenges** - **Limited accuracy** - **Managing mosaicisms** - **Concordance between trophectoderm biopsy (TEB) and inner cell mass (ICM).** - **Invasiveness of the procedure**
Opportunities	**Threats**
- **Increasing demand** - Increased access: PGT-A is becoming increasingly accessible to women over 40, particularly in countries with well-developed fertility treatment services. - **Adoption of elective single embryo transfer (eSET).** - **Reduction in Time to Pregnancy.** - **Advances in technology:** Advances in technology are continually improving the accuracy and effectiveness of PGT-A. - **Personalized medicine:** PGT-A can be used to provide personalized medicine for women over 40, allowing them to make informed decisions about their fertility treatment.	- **Controversy:** critics argue that it can lead to the discarding of potentially viable embryos. - **Regulatory challenges** - **Patient expectations** - **Emergence of new technologies** - **Market threats** - **Economic Threats** - **Ethical Threats** - **Emotional and Psychological Impact** - **Adverse obstetrical and neonatal outcomes and long-term effects**

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