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Review article:

Preimplantation Genetic Screening in In Vitro Fertilization (IVF): A Comprehensive Review of Ethical, Clinical, and Technological Developments

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Abstract

Preimplantation Genetic Testing for Aneuploidy (PGT-A) and Preimplantation Genetic Screening (PGS) have become indispensable tools in In Vitro Fertilization (IVF) to increase pregnancy rates and enhance embryo choice. Analyzing its application in spotting chromosomal abnormalities to reduce implantation failure, miscarriage rates, and the danger of genetic illnesses, this extensive research looks at the technological, clinical, and ethical sides of PGS. Screening techniques have developed to significantly improve accuracy and reliability from early Fluorescent In Situ Hybridization (FISH) to sophisticated Next-Generation Sequencing (NGS). Notwithstanding its benefits, PGS raises some ethical issues and therapeutic limitations, including the debate on genetic determinism, the influence of embryo biopsy on viability, and the likely misclassification of mosaics arising from mosaicism. Moreover, remaining challenges for many patients include PGS's cost burden and availability. As industry advances, non-invasive genetic testing, artificial intelligence-driven embryo selection, and ethical concerns are addressed, and CRIS pen-based genetic therapeutics might help improve IVF success be improved. This paper provides a reasonable evaluation of PGS's prospects, efficiency, and constraints, thereby directing its use in modern reproductive biology. This study aims to contribute to the ongoing discussion on improving IVF outcomes and ensuring ethical integrity in genetic screening by incorporating ethical problems and the most current studies.

Keywords: Preimplantation genetic screening, aneuploidy, IVF, embryo selection, genetic screening.

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1. Introduction

Among the most common assisted reproductive technologies (ART) meant to help individuals and couples overcome infertility is in vitro fertilization (IVF). Louise Brown changed reproductive medicine by offering a useful replacement for those unable to conceive naturally, the first IVF baby born in 1978 [1]. The technique fertilizes an egg outside the body under regulated laboratory settings, then implants a live embryo into the uterus, initiating a pregnancy [2].

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Preimplantation Genetic Testing for Aneuploidy (PGT-A) is a reproductive method meant to increase the effectiveness of in vitro fertilization (IVF) by spotting embryos with chromosomal defects before implantation. More generally now referred to as Preimplantation Genetic Screening (PGS). Selecting euploid embryos with the suitable chromosome count can enable PGT-A to raise implantation rates, lower miscarriage risk, and increase the likelihood of a healthy delivery. Rising IVF incidence in line with genetic testing technology developments has resulted in global PGT-A acceptance rising [3,4].

Although PGT-A has several advantages, ethical discussion regarding its use has been fairly lively. Opponents of choosing embryos based on genetic parameters question eugenics, discrimination against aberrant embryos, and the moral implications of throwing away damaged eggs [5]. Furthermore unavailable for many couples due to PGT-A's high cost fuels debates on the social and ethical consequences of genetic embryo selection [6].

Clinically, PGT-A's performance is still questionable. Although some studies claim PGT-A reduces the transfer of aneuploid embryos and increases live birth rates, others contend the surgery could unintentionally reject eggs appropriate for healthy pregnancies. The clinical dependability of PGT-A is further complicated by mosaicism, in which an embryo comprises both normal and aberrant cells, thereby casting doubt on its actual prognostic utility in reproductive medicine [5,7].

Although PGT-A's accuracy and efficiency have improved, acknowledging in large part technological innovations. By moving from fluorescence in situ hybridization (FISH) to next-generation sequencing (NGS), chromosome analysis has advanced, and the likelihood of misunderstanding has been reduced. Moreover, under development as fascinating alternatives to conventional biopsy-based methods are non-invasive embryo assessment methods involving analysis of wasted culture media. These advances might make PGT-A safer, more readily accessible, and more efficient [8].

This article aims to give a comprehensive review of the ethical, therapeutic, and technological improvements in PGT-A. Analyzing the existing situation of preimplantation genetic testing, its implications for reproductive medicine, and future directions lets this research contribute to the ongoing discussion on the purpose of genes in assisted reproduction.

2. Historical and technological evolution of preimplantation genetic screening

Originally known as Preimplantation Genetic Screening (PGS), Preimplantation Genetic Testing for Aneuploidy (PGT-A) has evolved fascinatingly since its introduction in the late 20th century. Originally meant to raise in vitro fertilization (IVF) success rates, PGS searches for chromosomally normal embryos before implantation, therefore lowering miscarriage rates and raising the chances of healthy children. PGS's evolution is closely linked with the developments in reproductive technologies, genetic testing techniques, and bioethical issues [9].

Genetic screening originated in the middle of the 20th century when cytogenetic methods were first used to examine chromosomal abnormalities. Prenatal genetic diagnosis (PGD) originated with the historic identification of the chromosomal basis of genetic diseases like Down syndrome (trisomy 21), Turner syndrome (monosomy X), and Klinefelter syndrome (XXY). Standard techniques for spotting genetic abnormalities during pregnancy during the 1970s were amniocentesis and chorionic villus sampling (CVS) [10].

Reproductive medicine underwent a sea change in 1978 when Robert Edwards and Patrick Steptoe

developed in vitro fertilization (IVF). The birth of Louise Brown, the first IVF child born outside of the human body, proved the viability of fertilization outside of the human body, therefore creating new assisted reproduction opportunities. PGS emerged in the late 1980s and early 1990s as IVF technology advanced, and researchers started investigating techniques for choosing healthy embryos before implantation [11].

2.1 The First Generation of PGS: Fluorescence In Situ Hybridization (FISH)

Early in the 1990s, PGS was initially found to be used in clinical settings using fluorescent in situ hybridization (FISH), a method that allowed certain chromosomes to be seen in embryonic cells. FISH uses fluorescently tagged DNA probes that attach to certain chromosomal areas to allow numerical chromosomal aberrations to be identified [12].

But FISH-based PGS has major restrictions. It could first only examine a small number of chromosomes (usually between 5 and 9), thereby providing an inadequate evaluation of aneuploidy. Often leading to misdiagnosis also affected the procedure low resolution, signal overlap, and technical unpredictability. Notwithstanding these drawbacks, FISH-based PGS gained popularity mainly among advanced mother age women having IVF [13].

2.2 Second-Generation PGS: Comparative Genomic Hybridization (CGH) and Single Nucleotide Polymorphism (SNP) Arrays

Early in the 2000s, advances in molecular genetics brought the technique known as comparative genomic hybridization (CGH), which lets all 23 chromosomal pairs be screened into use. CGH provided a more complete analysis of chromosomal aberrations than FISH, which had a more limited emphasis, therefore improving the accuracy of embryo choice [14].

Starting simultaneously with CGH, single-nucleotide polymorphism (SNP) arrays began to show considerable promise. SNP arrays provide high-density genomic profiling by means of single-nucleotide variations all over the genome. This approach improved the utility of reproductive genetics by allowing one to better recognize partial chromosomal abnormalities, uniparental disomy, and mosaicism [15].

2.3 The Current Era: Next-Generation Sequencing (NGS) and Non-Invasive Genetic Testing

Offering higher accuracy, faster results, and cost-effectiveness over previous methods, next-generation sequencing (NGS) in the 2010s changed PGS. Even low-level mosaicism and slightly changed genes are found by deep sequencing fetal DNA made feasible by NGS [16].

Furthermore, non-invasive preimplantation genetic testing (niPGT), which looks at DNA fragments the embryo leaves in the culture medium, has drawn a lot of interest recently. This technique eliminates the need for embryo biopsy and preserves great diagnostic accuracy, therefore reducing the risk of damage [17].

2.4 Whole Genome Amplification (WGA)

Preimplantation Genetic Screening (PGS) depends critically on a method called whole genome amplification (WGA), which lets one analyze genetic material from single or a few embryonic cells. Standard genetic testing techniques, which depend on a lot of DNA, are not practical since IVF-available embryos have just a limited number of cells. WGA addresses this by amplifying the whole genome of an embryo's biopsied cell(s), allowing downstream genetic analysis involving aneuploidy screening, single-gene disorder recognition, and chromosomal structural analysis [18].

Driven by the necessity to do genetic research on single blastomeres taken from early-stage embryos, the first effective WGA methods in reproductive medicine initially surfaced in the 1990s. Early WGA techniques derived from polymerase chain reaction (PCR), especially degenerate oligonucleotide-primed PCR (DOP-PCR), which allowed for extensive genome amplification. This approach has drawbacks, however, including preferential amplification of certain genomic areas, which resulted in either partial or biased representation of the genome [19].

WGA approaches have developed recently to assist microarray-based PGS and next-generation sequencing (NGS). Developed to reduce amplification bias and increase genome coverage are advanced WGA techniques like ligation-mediated PCR (LM-PCR), malting temperature PCR (MALBAC), and primer extension preamplification (PEP-PCR) [20].

3. Clinical Implications and Effectiveness of PGS in IVF

PGS and implantation rates are adopted extensively in assisted reproductive technology (ART), and preimplantation genetic screening (PGS) aims to raise implantation rates in vitro fertilization (IVF), still a great difficulty in IVF; implantation failure is usually ascribed to chromosomal defects in embryos. PGS seeks to raise the likelihood of successful implantation and later pregnancy by choosing euploid embryos, those with the ideal chromosomal count [21]. PGS improves implantation rates in several patient groups, especially with new technologies like next-generation sequencing (NGS) for aneuploidy identification, many studies have shown. Studies show that compared to conventional morphological selection, moving euploid embryos found by PGS produces far greater implantation success [22].

When examining the whole IVF cycle, several studies indicate that PGS does not always raise cumulative pregnancy rates, even as it may boost implantation rates per embryo transfer. Furthermore, the intrusive character of embryo biopsy for PGS has generated questions about possible harm to embryos, which could, in some situations, ironically lower implantation chances [23].

Reduction of pregnancy loss and miscarriage risks, particularly in women undergoing IVF, is a significant cause of early pregnancy loss is aneuploidy, or aberrant chromosomal makeup. PGS is meant to lower miscarriage chances by screening embryos for chromosomal defects by ensuring only chromosomally normal embryos are implanted [24].

Studies show that PGS greatly reduces first-trimester miscarriage rates as compared to traditional IVF. Women who had PGS reported a miscarriage incidence of 7.9% compared to 20% in those who did not have genetic screening, according to a 2013 Harton et al. research. Patients who have a history of recurrent miscarriage or implantation failure can especially benefit from this [25]. These results nonetheless have some researchers wondering if PGS offers a statistically meaningful drop in miscarriage rates for younger women or those with large ovarian reserves. PGS may not be required for patients who currently generate high-quality embryos with little risk of aneuploidy, some experts contend [9].

PGS has as its main goal increasing live birth rates by means of chromosomally normal embryo transfer, while selecting euploid embryos to improve live birth rates. Studies show that PGS may be associated with improved live birth rates, particularly in cases with advanced genetic screening techniques such as next-generation sequencing (NGS) [15]. Concurrently, randomized controlled trials (RCTs) have shown contradicting results. Although some studies show a higher cumulative live birth rate per IVF cycle, others

argue that PGS may not meaningfully increase overall live birth rates in certain populations [26].

PGS in advanced maternal age and Recurrent Pregnancy Loss (RPL), key candidates for PGS include women of advanced mother age (AMA) and those experiencing recurrent pregnancy loss (RPL). Older women run the risk of generating aneuploid embryos, hence genetic screening is a useful technique for choosing an embryo [13]. Some studies, however, contend that rejecting embryos depending on PGS findings may lower pregnancy chances in women with restricted embryo availability, therefore negating the advantages of PGS [27].

Challenges in accuracy and false positives/negatives, Preimplantation Genetic Screening (PGS) presents one of the main difficulties in terms of the possibility of erroneous findings that would cause false positives, misdiagnosing normal embryos as abnormal, or false negatives, failing to identify aneuploidy. False positives might cause the needless disposal of healthy embryos, therefore lowering the pregnancy odds, particularly in limited embryo availability [28]. Conversely, false negatives may cause miscarriage, implantation failure, or the delivery of a child with undetectable chromosomal defects [29].

Mosaicism, where embryos have both normal and aberrant cells, makes diagnosis challenging and is a major contributor to these mistakes. Though current research reveals some may grow into healthy live births, earlier PGS techniques often misclassified mosaic embryos as entirely defective [30]. PGS accuracy is influenced by limited biopsy samples, technical constraints, and embryonic self-correction; over-reliance on genetic testing is called into question [31]. Future advancements that optimize embryo choice in IVF and raise PGS accuracy might include non-invasive genetic testing (niPGT) and artificial intelligence-driven embryo assessment [32].

4. Ethical and social considerations in preimplantation genetic screening

Particularly concerning embryo selection and disposal, preimplantation genetic screening (PGS) raises major moral conundrums. Before implantation, screening embryos for chromosomal abnormalities raises moral questions about the status of embryos and whether it is ethically justified to discard aneuploid embryos. Critics argue that PGS encourages eugenics-like approaches in which embryos are chosen based on genetic fit, therefore fostering discrimination against those with disabilities [6]. Moreover, false positives in PGS might lead to the unnecessary removal of viable embryos, hence increasing ethical issues concerning fertility treatments [33].

The legal condition of PGS varies widely depending on the country; some governments restrict its use for ethical concerns, while others permit it under strict medical criteria. In the United States, PGS is regulated under general assisted reproductive technology (ART) guidelines; no national law especially governs its use. On the other hand, in Germany and Italy, tight rules restrict embryo screening to situations where there is a high chance of serious genetic problems, therefore reflecting a more cautious posture [34]. Lack of worldwide agreement on PGS control raises questions about medical tourism, in which patients visit nations with more liberal regulations in order to get genetic testing [35].

Religious and cultural considerations of PGS are seen from somewhat different religious angles. Because life starts at conception and believes embryo selection and disposal to be immoral, Christianity, especially Catholicism, opposes PGS [36,37]. Islamic opinions on PGS differ; some researchers warn against its ethical consequences, while others allow it under specific circumstances,

especially when it helps to avoid serious genetic diseases [38]. Emphasizing the notion of pikuach nefesh, that is, preserving a life, Jewish law typically favors PGS when used to prevent inherited disorders. Concerns about karma and the dignity of life shape ethical discussions on embryo selection in Hindu and Buddhist traditions. Different religious and cultural perspectives influence PGS accessibility and acceptability all over [39].

Psychological and societal impact on parents' perspective, PGS may have a major psychological impact that shapes their emotional well-being, decision-making, and view of pregnancy. Particularly if many IVF cycles are needed to find a genetically "ideal" embryo, the capacity to choose embryos according on genetic screening might generate great expectations and anxiety [40]. Should an embryo be discarded based on PGS results, parents may experience guilt or regret, especially given the possibility of false positives leading to the loss of maybe viable embryos. Moreover, societal pressures around "designer babies" and genetic alteration contribute to ethical problems about PGS being utilized outside of medical necessity, therefore promoting probable prejudice against persons with disabilities [41].

5. Conclusion

Preimplantation Genetic Screening (PGS), Preimplantation Genetic Testing for Aneuploidy (PGT-A) has significantly transformed the area of assisted reproductive technologies (ART). PGS, especially for patients with advanced mother age, recurrent pregnancy loss (RPL), and repeated implantation failure (RIF), aims to raise implantation rates, reduce pregnancy loss, and enhance live birth rates by allowing the choice of chromosomally sound embryos before implantation. From early fluorescence in situ hybridization (FISH) techniques to current next-generation sequencing (NGS) and non-invasive preimplantation genetic testing (niPGT), continuous technological improvement has improved the accuracy of embryo selection. Still, current challenges include false positives and false negatives as well as the consequences of mosaicism and the risk of rejecting living embryos.

Beyond mere clinical efficacy, PGS raises ethical, legal, and social issues, particularly about embryo selection, accessibility, and reproductive autonomy. The debate on the moral stance of embryos, the potential of eugenics-like techniques, and variations in international policy underlines the need of ongoing ethical review. Moreover, impacting public acceptance and government decisions are religious and cultural perspectives, so different PGS methods are used worldwide. Moreover, underscored by the psychological burden on prospective parents, including stress associated with decision-making and social expectations, are the requirements of informed consent and ethical counseling in reproductive medicine.

Although PGS has some benefits in improving IVF outcomes, its effectiveness is still debatable, particularly for younger patients and those with few embryos. Reducing invasiveness, increasing diagnostic accuracy, and adding artificial intelligence (AI)-driven embryo selection would allow PGS to optimize clinical outcomes. Striking a balance between scientific successes with ethical responsibility, equitable access, and individualized patient care will help PGS remain a valuable tool in reproductive medicine without compromising ethical ideals as technology improves.

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