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REVIEW ARTICLE

Preimplantation Genetic Diagnosis in India: The Current Scenario and Potential Developments

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Abstract Preimplantation genetic diagnosis (PGD) is the selective process undertaken during the in vitro fertilisation (IVF) procedure to diagnose genetic abnormalities in the embryos using various genetic techniques and implant only those embryos that are devoid of genetic abnormalities. It was established in the 1990s and is still a developing technology in India. This review summarizes the need for widespread and competent PGD centres equipped with advanced diagnostic techniques to reduce disease burden upon the country's economy and the requirement for sufficient education of the general population on the advantages of PGD. Issues such as high frequency of consanguinity and genetic disorders such as hemoglobinopathies especially thalassemia can be addressed with the use of PGD. There also needs to be awareness campaigns that help enhance knowledge in this field to improve its use such as reducing the dilemma of increased congenital anomalies in consanguineous unions and prevent its misuse such as preimplantation sex selection and sex based discrimination.

Keywords Preimplantation genetic diagnosis · Assisted reproductive techniques · Fluorescent in situ hybridization · Thalassemia · Sex selection

Introduction

Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) are in vitro techniques wherein few cells of the blastocyst or embryo, or polar bodies are extracted for genetic analysis before implantation into the uterus [1].

These techniques were developed in the 1980s. The first reported successful pregnancy and birth of a normal baby girl occurred in 1992 which involved detection of a gene deletion associated with cystic fibrosis. The procedure was performed by Handyside et al. at the Royal Postgraduate Medical School at Hammersmith Hospital in London, UK [2].

A recent study undertaken in the UK cleared the implication that PGD increased the frequency of pre-term birth and low birth weight using data collected from the Human Fertilisation and Embryology Authority (HFEA), UK regarding singleton birth after in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) treatment during 1996–2011 [3–5].

An advantage of PGD/PGS in India is that it reduces religious and ethical dilemma. Detecting the genetic abnormality during the preimplantation stage reduces the need for abortion and/or occurrence of complications during pregnancy hence, reducing trauma to the mother.

This technique as advantageous as it is, must be strictly regulated especially in India where sex-based discrimination and female foeticide are rampant. Hence, license to perform PGD/PGS is regulated by law. Sex selection due to non-medical reasons is also tightly regulated in many other countries like China, some regions of Australia and some European countries. The situation regarding PGD/PGS in India is much more lenient than in countries like Ireland,

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Austria, and Switzerland where PGD/PGS is prohibited or has only recently been made legal [6].

Terminologies

In PGD, embryos of at-risk couples are tested for their genetic composition. The embryos devoid of genetic aberration are implanted into the uterus. Some commonly tested diseases are cystic fibrosis, Tay-Sachs, fragile X syndrome, muscular dystrophy and thalassemia.

PGS is a variant of PGD involving embryo screening from chromosomally normal parents for a panel of genetic aberrations which may be involved in miscarriages or infertility to increase the chances of a successful pregnancy. It involves negative selection of embryos carrying aberrations. 50% of miscarriages involve some form of chromosomal defect. Aneuploidies are a leading causes of miscarriages and implantation failure [7].

Although widely used even today, the terms PGD and PGS, as of 2017, have been replaced by the term preimplantation genetic testing (PGT) according to 'The International Glossary on Infertility and Fertility Care, 2017'. A consensus was taken by The International Committee for Monitoring Assisted Reproductive Technologies (ICMART) in association with several prominent societies involved in human reproductive medicine to define several terminologies including PGT which is stated as "A test performed to analyse the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA-typing or for determining genetic abnormalities". There are three subdivisions: PGT-A refers to testing for aneuploidies, PGT-M for monogenic/single gene defects and PGT-SR for chromosomal structural rearrangements [8].

Biopsies Techniques for PGT

The PGT process begins with a biopsy. The cells biopsied depend on the stage at which the procedure is performed and type of screening to be undertaken. Over the years, several chemical, mechanical and laser techniques have been invented for drilling the zona pellucida with minimal loss of healthy embryos due to complications during the extraction [9].

Commonly 1–2 blastomeres are extracted from day-3 morula formed when the zygote begins cleaving giving a fluid-filled sphere of 5–8 cells. The only concerns are the risk of mosaicism and cell mass reduction. However, studies show that polar body and day-5 trophectoderm biopsy processes reduced rates of complications compared to blastomere biopsy. The procedures also present fewer ethical conflicts as trophectoderm biopsy involves extraction of cells that would give rise to placenta and fetal membranes. Similarly, polar bodies have not been reported to play a constitutional part in foetus development [6, 10].

A polar body biopsy would suffice if the father is known to be unaffected by the suspected disorder. This process has better success rates and prevents unnecessary loss of healthy embryos due to complications [11].

But each technique comes with its own pitfalls. Polar body biopsy provides knowledge of only maternal genes and has dubious diagnostic accuracy as blastomeres carrying aneuploidies, have a high incidence of self-correction which cannot be detected by polar body biopsy.

Trophectoderm biopsy can be used to detect abnormalities in both maternal and paternal tissues and studies have suggested that it leads to better implantation and live birth rates than cleavage stage biopsy. Up to 4–20 cells can be aspirated which provides a definitive advantage over blastomere biopsy. But the drawback is that of time available for genetic testing as delayed embryo transfer may lead to unsuccessful implantation. This problem may be solved by efficient vitrification and thaw-revival cycles [12].

Genetic Analysis

To prevent passing on the defective genes, the concerned parents need to undergo thorough genetic counselling and following that, PGS for their embryo. The screening is done by techniques such as fluorescent in situ hybridization (FISH), array comparative genome hybridization (CGH), comprehensive chromosome screening (CCS) etc. FISH probes are available for the commonest aneuploidies such as trisomy 21, 13, and 18, Turner and Klinefelter syndromes. FISH has been one of the most widely used techniques since the discovery of PGT but there have been reports suggesting a decrease in implantation rates when it was opted. Some of the other reported drawbacks were hybridization failure, signal overlap, signal splitting and difficulty in blastomere fixation. This has been countered by advancements in technology, equipment and handling of embryos as well as development of comprehensive genome analysis using array CGH and single nucleotide polymorphism (SNP) arrays [13, 14].

PGT can also be performed for diseases caused by mitochondrial DNA (mtDNA) aberrations. Individuals with a history of mitochondrial disorders can undergo PGT to determine if the oocyte or embryo carries the mutated mtDNA. The embryo with optimal genotype can then be implanted. However, reliability of this procedure in humans is vague [15].

PGT in India

In India, PGD is supervised by the Ministry of Family Health and Welfare. According to the Pre-Conception and Prenatal Diagnostic Techniques Act of 1994, a written consent specified by the guidelines in a language understood by the individual must be obtained before PGT.

There have been many cases of successful PGT application in India since its introduction. In 2015 Selvaraj et al. reported the first documented successful birth of twins in south India after PGS using array-CGH [16].

The number of clinics and diagnostic centres that have acquired state-of-art technology and expert clinicians specializing in PGT in India have been increasing steadily. Oasis India performs PGS for all 23 chromosomes using array-CGH. They perform both blastomere and trophectoderm biopsy and claim to provide reports within 36 h of screening ensuring a fresh blastocyst transfer. Iswarya Fertility Centre uses Next gen sequencing for PGT and boasts a 100% genetic detection rate. They also provide PGS panel for carriers of inversions. Delhi IVF & Fertility Centre (DIFC) even involve a specialist team from Spain to carry out PGT. Nova IVI Fertility is a leading chain of fertility centres with clinics present all over India such as Mumbai, Delhi, Chennai, Kolkata, Surat, Ahmedabad with a state-of-the-art clinic opening recently in Lucknow. Besides PGT they also provide a personalised genetic test to determine the state of endometrial receptivity called Endometrial Receptivity Array (ERA) for patients who have had repeated implantation failure despite a diagnostically normal embryo and uterus [17–20].

PGT for Single Gene Disorders

PCR is the technique commonly used to detect single gene disorders Huntington's chorea, sickle cell anaemia, albinism, cystic fibrosis, Duchenne muscular dystrophy etc. Many developments have been seen in this field including SNP arrays and CCS.

Most centres require a pre-PGD work-up wherein complete history and blood tests are taken to design a protocol specific for the patient. Furthermore, unique gene sequences are identified from each parent that would be transmitted to the progeny to rule out DNA contamination. Pre-PGD work-up can involve HLA typing which is used to find a matching donor in cases of blood disorders like hemoglobinopathies, aplastic anaemia, leukaemia, hemochromatosis etc. [7, 21, 22].

Congenital deafness afflicts on average 6.3% of the Indian population. It is inherited in an autosomal recessive manner in 50% of the cases, autosomal dominant late-onset or X-linked disorder manner in some and rarely due to mitochondrial inheritance. An asymptomatic couple have a 16% increased chance on average of having a second affected child if their first born is affected. PGT can be used to diagnose syndromic and non-syndromic hearing loss, preventing significant co-morbidity due to cochlear implants and testing. Each implant costs around 1–5 lakhs and the treatments are accompanied by lifelong care and rehabilitation which seems considerably expensive juxtaposed with PGT and IVF. The success rates though, of most IVF cycles, are $\sim$ 25–30% [3, 7].

Many studies show that PCR and FISH, despite being the most widely used approach for genetic profiling of embryos, don't provide complete information. This limitation can be overcome by whole genome amplification (WGA) which facilitates multi-gene multi-loci screening and provides enough genetic material for confirmatory tests. It has a faster turnaround time which helps preserve embryo viability. This approach was used by Akanksha Hospital and Research Institute in Gujarat for screening embryos for the presence of adverse genetic mutation(s) in the COL4A1 gene for which the father was a known carrier. COL4A1 gene, located on the q arm of chromosome 13 in humans, codes for Type IV collagen alpha 1. Dominant mutations in this gene may lead to highly penetrant cerebrovascular diseases and hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome. Trophectoderm biopsy and WGA resulted in successful implantation of embryo free from COL4A1 gene mutation after several screening cycles. Chorionic villus sampling at 11th week of gestation was performed for confirmation [23].

PGT for Hemoglobinopathies

Hemoglobinopathies like thalassemia and sickle cell anaemia are the most prevalent inherited disorders in the Indian population. But PGS for such single gene disorders is not widely available [7].

It has been estimated that around 7% of the world's population are carriers of some form of thalassemia which is prevalent in the Mediterranean area, Middle East, Transcaucasia, Central Asia, Indian subcontinent, and Southeast Asia [24, 25]. It is an autosomal recessive disorder involving mutation in the β globin gene. Both homozygotes and compound heterozygotes present with severe anaemia necessitating repeated blood transfusion and expensive iron chelation therapy. Approximately 10,000 babies are born in India annually affected by β-thalassemia with an estimated 40 million carriers in the current population. But despite collaborations with societies such as Red Cross and The International Thalassemia Federation, patient care cost is high and requires lifelong monitoring hindering the quality of life. Therefore, care for thalassemia has been included in the 12th 5-year plan by

the Government of India. Some states have made chelation therapy and blood transfusions free of cost [26].

ThalInd is a database created by collaboration between administrative health system and demographic resources of the country containing information on thalassemia mutations prevalent in the Indian population, infrastructural assessment, genotype–phenotype correlations etc. There have also been studies reporting data on rare mutations. Hence, there's a need to improve availability and speed of cost-efficient PGS using the available information.

The first successful PGT pregnancy in India occurred in 2012. The parents were carriers of β-thalassemia gene mutation and had a thalassemia major affected child. They previously had two medical terminations of pregnancy which were revealed to be thalassemia major upon prenatal diagnosis. The mutation analysis for the parents was performed by ARMS-PCR followed by PGT for the embryo in two consecutive IVF cycles. The embryo carrying thalassemia minor gene, was implanted and subsequent confirmation was done during prenatal diagnosis [27].

Another option is to give birth to a saviour sibling after PGT who is an HLA match to the affected child. In such cases, chances of curing thalassemia by bone marrow donation and hematopoietic stem cell transplant is 100% [28].

But there hasn't been enough data on the development or establishment of centres performing HLA typing along with PGT in India [29].

PGT for Chromosomal Abnormalities

The use of PGT for chromosomal abnormalities has been reported only a handful of times in India. PGT can prevent miscarriages caused by chromosomal abnormalities wherein the parents are carriers of balanced inversion or translocation. Studies show that PGT has reduced the rate of translocation related pregnancy loss from > 90 to $\sim 15\%$. Another report stated the first successful pregnancy and birth of a normal child after PGT for a reciprocal translocation in India in 2014 [21, 26, 30].

Dilemma of Consanguinity in India

Consanguinity is the mating between individuals who are second cousins or more closely related. It can lead to increased frequency of genetic abnormalities. In countries like India and many Arab nations, consanguinity is common practice even today.

Consanguinity has been associated with higher incidences of autosomal recessive disorders and major disorders like Down syndrome, heart abnormalities such as atrioventricular septal defect (AVSD), reproductive disorders, sterility, multifactorial psychological disorders such as bipolar disorder and depression and can even contribute to spontaneous abortions and stillbirths. The increase of mutated gene pool combined with limited resources, diagnostic, and management capabilities increases the disease burden for the country.

It's essential for consanguineous couples to undergo genetic testing, especially if their first child is affected. PGT helps in avoiding trauma to the family and provides a clearer picture of available options [31].

A review in 2007 described how the government and medical industry are trying to increase awareness by national newborn screening and established PGT at several centres in the Middle East and Northern Africa, considering the high level of consanguinity in these regions. Such an initiative could decrease the incidence of consanguinity-associated genetic abnormalities [32].

Lack of sufficient education on the detriments of consanguinity can lead to frequent genetic aberrations. Hence, government along with non-governmental organizations, can devise targeted awareness programs involving genetic counselling and prenatal diagnosis [24].

Sex Selection and PGT

Since the advent of PGT, testing has moved on from risk diagnosis of common disorders to HLA compatibility typing, sex selection, hereditary cancer genes mutation detection, late onset disorders such as Alzheimer's disease.

But for obvious reasons sex selection via PGT should be strictly controlled in India. Although prenatal sex selection is practiced in countries such as the USA, in countries like India, China, Bangladesh, and Pakistan it is illegal as it can cause a sex ratio imbalance. This issue goes hand in hand with discriminatory customs like inheritance, dowry etc. Nevertheless, PGT isn't feasible to be used for only sex selection purposes due to the cost which can go over 1 lakh per cycle with only a 25% success rate. Additionally, success rates are even lower following embryo sexing.

Some couples opt for sex selection for the sake of 'balancing' or 'family planning'. Despite this concept not having a 'sexist' dilemma, it seems trivial compared to the use of PGT for eliminating disorders that will affect the quality of life. As of the amendment in 14th February 2003, The Pre-Conception and Pre-Natal Diagnostic Techniques (Prohibition of Sex Selection) Act prohibits use of sex selection at 'any stage of fertilisation' except to eliminate genetic, metabolic, X-linked abnormalities and/or hemoglobinopathies [33–35].

Cost and Availability of PGT in India

The number of centres with established micromanipulation and vitrification setups necessary for successful analysis

and implantation should be increased throughout India. ICSI must be performed for every PGT which considerably increases the cost. But scientists would argue that the cost is affordable compared to the life-long complications and trauma caused by an affected child and it help to avoid maternal trauma. But this is only advantageous if live birth rates are relatively higher.

Multiplex PCR and FISH are considered the gold standard for PGT. Concerned parents need to be thoroughly counselled about the diagnostic techniques available at the preimplantation stage and the risks involved in PGD and IVF [13, 36].

Reproductive Tourism in India

Reproductive tourism or 'reproductive exile" is when couples travel to other countries seeking successful conception and pregnancy. This can be due to deficit of adept ART facilities within their country or legal complications.

A major form of tourist attraction in India has been the reproductive medicine field and ART establishments—an industry that attracts a great number of foreign clientele. This may be due to lax surrogacy laws, cheaper costs and availability of advanced techniques compared to poorer countries in the last 10 years. Many IVF facilities' websites overtly suggest services tailored to attract foreign clients such as visa applications, surrogacy services, international adoption etc. According to a report it was stated that Mumbai, the financial centre of India, has the most number of infertility clinics that offered services especially suited for foreign clientele.

PGT was suspected to be one of the main sources for reproductive tourism, since it solves many ethical issues and isn't as tightly regulated in India as it is in many other countries. But the cities containing the major IVF facilities offering PGT attracted an equally large number of domestic tourists. Hence, it was concluded that PGT may be seen as being marketed largely towards the Indian population than to foreigners [37].

Conclusion

A reason why PGT may not be practiced more frequently might be because molecular studies are performed only during prenatal testing. They couple may not know their carrier status or even the possibility of PGD. There also needs to be discussions on reducing misdiagnosis during genetic counselling before PGT. Furthermore, the cost can climb depending on number of IVF cycles required for successful implantation.

Studies on marketing of services show that some IVF websites suggest false or incomplete information regarding statistical data, that may lead clients to assume that PGT is more successful than what is true (e.g. depicting implantation and conception rates rather than successful pregnancy or delivery rates) suggesting questionable strategies to provide a positive perception of rates which may hinder the development of more successful techniques [38].

ISO 15189 provides standards internationally for medical laboratories. An accredited PGT diagnostic laboratory must conform to those standards, work in partnership with IVF centres and is required to participate in external quality assessment schemes.

The upside is that several major advancements are being made presently. Many fertility centres provide affordable options of IVF and PGT, such as EMI for a limited number of cycles. It's been observed that the cost and time required (in terms of IVF cycles) to achieve a successful pregnancy despite history of RPL has been significantly reduced when IVF was coupled with PGT. PGT has been reported to significantly shorten the time taken to achieve a successful pregnancy from 4 to 6 years to < 4 months, and decrease miscarriages from > 90 to $< 15\%$ for translocation carriers [14, 30].

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