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ETHICAL ISSUES IN PRE-IMPLANTATION GENETIC TESTING

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Ethical Issues In Pre-implantation Genetic Testing

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INTRODUCTION

Fertility treatment is no longer limited to routine procedures like IVF/ICSI. Now, it offers the option of evaluating the genetic status of the embryos through pre-implantation genetic testing. It helps select euploid embryos, thereby, facilitating elective single embryo transfer (eSET) and minimising risks involved with multiple gestation.

What exactly is PGT?

Pre-implantation genetic testing (PGT) evaluates the DNA content of an embryo and thus, helps in screening the embryos for genetic defects. It has three types, namely:

1. PGT-A (earlier known as PGS)
2. PGT-M (earlier known as PGD), and
3. PGT-SR

In simple words, PGT-A screens for numerical chromosomal aberrations, PGT-M is meant for identifying monogenic disorders (sex-linked disorders, single gene defects) and PGT-SR is used to check for structural abnormalities in the chromosomes, like rearrangements.

Who should opt for PGT?

Indications of PGT:

1. couples with severe male factor infertility,
2. females with advanced maternal age (above 35 years of age),
3. the ones who have experienced recurrent implantation failure or pregnancy losses (Wang et al., 2010).
4. Any or both partners with abnormal karyotype
5. History of monogenic disorder running in the family
6. History of any mutation in previous pregnancy

What are the advantages of PGT?

1. PGT increases the chances of pregnancy as euploid embryos have a higher chance of being accepted by the uterus and thereby, implanting successfully (Brezina et al.,2012).

2. It also provides the possibility of conception of normal, unaffected children to the couples with known genetic disorders (Sermon et al., 2004)

3. It helps decrease the chances of multiple pregnancies as elective single embryo transfer (eSET) is more viable.

4. It reduces the risk of miscarriage and the subsequent pregnancy loss thereby, increasing the IVF success (Meldrum, 2013).

Global status on PGT

The current scenario for PGT showcases it as an interaction of two complex technologies, that is, assisted reproductive technology and genetic testing which are associated with a complicated regulatory status (Hudson, 2006). Hence, it is not surprising that various legal, social and ethical issues stem from this revolutionary technique. Different countries hold different opinions regarding PGT viz; the Netherlands, United Kingdom, France and Spain are considerably legally liberal towards it whereas Italy, Germany, Austria and Switzerland have restrictive laws prohibiting PGT with little space for legal loopholes and exceptions (Kuliev, 2012).

In India, sex selection using PGT is entirely prohibited as per PCPNDT Act, 1994, amended in 2003. There are no restrictions on the number of embryos to be used but strict regulations are in place to prevent its gross misuse.

PGT: A double- edged sword

Despite numerous advantages of this emerging technology, PGT still continues to be criticized by many. Some of the ethical concerns with PGT are:

1. Is it safe?

Invasiveness of the technique raises concerns regarding the procedure as well as the developmental competence of the embryo. In blastomere biopsy, there is a loss of a significant amount of cytoplasm which can hamper the embryo's ability to form a blastocyst (Bar-El et al., 2016). Although, literature supports biopsy of trophectoderm cells which are destined to form the placenta, grave consequences arise if excess cells are removed. Studies have reported that embryos with higher DNA content in biopsy material have a lower pregnancy outcome (Neal et al., 2017).

2. Misdiagnosis

Misdiagnosis is one of the greatest challenges with PGT. Studies on PG testing have shown that as many as 50% of cleavage stage embryos exhibit mosaicism (a condition in which a single embryo has a mixture of normal and abnormal cells). Therefore, one biopsied blastomere may not represent the ultimate chromosomal status of the foetus (Brezina et al., 2012).

It has been documented that even at the blastocyst stage, there is a lack of consistency between the inner cell mass cells and the trophectoderm cells (Kushnir et al., 2018). Owing to these shortcomings, amniocentesis still continues to be the gold standard to confirm the genetic makeup of the foetus once the pregnancy is achieved (Forman et al., 2012; Vaiopaulos et al., 2013; Harton et al., 2017).

3. Moral and legal status of the embryo

This issue has two arguments :

a) The embryo is a new human life granted complete moral status (the basic right to life as an individual) from the time of fertilization, because from that time, it holds the potential to develop into a complete human being.

b) The embryo has some moral status from fertilization, but to an extent lesser than a born human being, and gradually achieves complete moral status during its development (Knoppers et al., 2006).

   For those who hold the latter view, like in India, there is no agreement as to when the embryo or the foetus achieves complete moral status (Mittal, 2013).

4. How much information is too much information?

Couples undergoing fertility treatment are particularly vulnerable in their decision making. They already go through a difficult time accepting infertility and possibly have experienced recurrent cycle failures and might get overwhelmed when too many scientific terms are put before them. This has implications for genetic counselling as they could rely heavily on the clinicians in making choices (Hens et al., 2013). So the question that arises is how much information should be disclosed to the couple to help them make an informed decision?

5. An embryologist's predicament

a) A serious ethical dilemma for an embryologist arises in situations like non-disclosure PGT where PGT-M is offered to the couple without them being ever informed of the test results. Their embryos are, therefore tested without revealing any of the details of the cycle or diagnosis. In cases where there are no "normal" embryos available for transfer, the embryologist faces a tough choice as to whether to perform a mock transfer or to cancel the cycle. Cancellation of the cycle will, however, breach the agreement between the embryologist and the patient by letting them know (even if indirectly) about their own carrier status (Robertson, 2003; Ethics committee, ASRM, 2013).

b) In some cases, after a PGT-A, couples are left with no euploid embryos available for transfer. However, some couples do insist on transferring these embryos. Given the instances where healthy live births have been reported following transfer of aneuploid embryos (Darilek et al., 2018) it becomes morally burdensome for the embryologist to decide whether to abide by the couple's decision or not.

6. Choosing the best embryo

Procreative beneficence is a theory that states that couples are morally obliged to choose an embryo whose life is expected to be the best. However, the higher the amount of information that is made available about an embryo, the tougher these choices may become. The possibility that each embryo may have a number of genetic abnormalities, either related to its viability in the uterus or to its health, either congenital or later in life, might create circumstances where tough decisions will have to be made by the couple or by the embryologists / clinicians involved (Savulescu and Kahane, 2009).

7. Use of PGT for HLA matched sibling donor (Creating a life to save a life?)

HLA matching to an existing sick child makes it possible for a couple to bear another child who can serve as a matched hematopoietic stem cell donor for the sick child. The first such case was about a family with a child who had Fanconi anemia. In this case, PGT-M was undertaken to select unaffected embryos, which had the same HLA type as the affected sibling. This application of PGT-M is highly controversial. The ethical concern here is that a child is being used as a treatment. A detailed counseling by a psychologist should be arranged before the use of PGT-M for this purpose to ascertain the real motivations of the potential parents (Burgio et al., 2012; Shapiro, 2017).

8. A boy or a Girl? (Sex Selection)

Sex selection through PGS also faces the problem of being a comparatively trivial reason for creating and selecting embryos. If it is carried out on a large scale, it could lead to great disparities in the sex ratio of the population.

9. Monopoly of the rich?

The entire procedure of Pre-implantation testing is an add-on expense to the existing treatment cycle as it requires entirely separate lab set-up to perform the procedure with the involvement of a third- party genetic testing lab for the diagnosis. This is what makes the procedure extremely expensive, indirectly allowing the financially privileged benefitting from it.

10. Contamination

Since PGT is an invasive technique, the embryo becomes vulnerable to maximum contamination as the protective layer (zona pellucida) of the embryo is breached.

There is an additional risk of DNA contamination while working with biopsied material and tubing. So, even a small lapse in aseptic technique can render the entire process futile (Capalbo et al., 2016).

11. Repeated biopsies

Blastocyst biopsy and vitrification-warming procedures are a critical part of PGT. Since, there are known technical glitches associated with the outcome pertaining to PGT, there are several instances where the results are inconclusive. In such cases, many embryologists as well as the couples opt for a re-biopsy of the embryos. Studies show that retesting of such embryos that fail to produce a result in the first attempt significantly reduces their pregnancy potential (Bradley et al., 2017).

12. Is PGT infallible?

A considerable amount of effort is put into selecting the best embryo for transfer in terms of the financial burden, the expertise of the embryologist, and time spent on procedures. In spite of PGT, there's no guarantee of a successful pregnancy and a normal child. This can be due to several reasons like :

a) allele dropouts,
b) detection of limited range of monogenic diseases,
c) false positives,
d) DNA contamination,
e) de novo mutations and mosaicism.

Technical limitations include:

a) Overlapping FISH signals,
b) Hybridization failure,
c) Non-specific hybridization and
d) The difficulty of interpreting closely adjacent signals (Harper et al., 2012).

Several other factors also contribute to an unsuccessful cycle such as inadequacy in receptivity of endometrium, the invasiveness of the biopsy process, skills of the embryologist and subjecting the embryo to the vitrification- warming process.

Also, healthy live births have been reported following transfer of aneuploid embryos which raises the question as to whether the embryos that are labelled as aneuploid after a PGT-A can be transferred in the absence of euploid ones (Darilek et al., 2018).

13. PGT: birth and beyond

There also arises a concern about the care of a child born after the PGT-A/ PGT-M procedure. Maximum couples get tested for genetic conditions only when the symptoms begin to appear and if such individuals do have a child through ART, what is likely to happen if the parent is not in a position to take care of the child or may be, isn't even alive to see the child grow. This situation not only poses a challenge about the upbringing of the child but also concerns the emotional trauma that the child may have to bear due to loss of a parent or both (Ethics Committee, ASRM, 2013).

Conclusion: To biopsy or not to biopsy?

Determining whether PGT is ethically acceptable or not, is highly subjective. It continues to be a controversial prospect. With the advancements in this field, the risks associated with this technique are being overridden, with advantages outweighing the concerns. The upcoming diagnostic methods are more sensitive and accurate, requiring lesser biopsied material for the screening. Attempts are being made by the embryologists to make the biopsy procedure safer and gentle on the embryos. The technology has come a long way and future may be of non-invasive pre-implantation genetic testing (niPGT) as the recent discovery of DNA in blastocoele fluid (BF) of blastocysts and in spent media looks promising.

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