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Gene Therapy or Preimplantation Genetic Diagnosis? 'Take Your Pick'

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Abstract: Most parents desire to have their own biological children who are healthy and free from genetic diseases. Now, with innovations in medical technologies such as gene therapy and preimplantation genetic diagnosis, the birth of children with genetic diseases may be successfully achieved. Although the ways in which both technologies work differ, the end result remains the same, that is, to ensure the birth of children who are free from genetic diseases. Both techniques, however, involve numerous legal, ethical and religious concerns that should be scrutinised before. This is the main crux of this paper where the common issues surrounding both technologies are carefully analysed with particular reference to Malaysia. It is concluded that an appropriate legal mechanism should be implemented in Malaysia so as to regulate these technologies and protect society against any potential perils.

Keywords: Gene Therapy; Crispr-Cas9; Preimplantation Genetic Diagnosis; Islamic Bioethics; Crispr-Cas9

1. Introduction

The advancement in medical technologies, including in the area of assisted reproductive technology, brings tremendous benefits to individuals and society. Other than offering hope for infertile couples to conceive, assisted reproductive techniques have also pave the way towards producing children without genetic diseases [1]. This goal can now be achieved by technologies such as gene therapy and preimplantation genetic diagnosis (PGD). Nonetheless, both techniques have their own perils. Although the ways in which both techniques operate differ, they share some common legal and ethical concerns which are identified and analysed in this paper. In the end, this paper further analyses whether a specific law should be introduced in Malaysia on the use of gene therapy and PGD. First, however, the science of both techniques is briefly presented. This is followed by an analysis of some of the mutual issues surrounding both technologies. Finally, this paper concludes and suggests for the introduction of a suitable legal framework to regulate both techniques in Malaysia.

2. Materials and Methods

This paper adopts a pure legal doctrinal method where analysis is made based on primary and secondary resources such particularly journal articles and case laws.

3. Discussion

3.1. *The Science*

Gene therapy and PGD both work at the embryonic level but not in the same ways. The former is used to modify the DNA of the embryos or cells while the latter merely selects the desired embryo without any alteration to its DNA or other features. In what follows, the science for both techniques is explained.

3.1.1. PGD

PGD can be considered as an alternative to other forms of pre-natal diagnosis such as Amniocentesis and Chorionic Villus Sampling (CVS). Amniocentesis and CVS can be morally problematic as they may result in the termination of pregnancy should the fetus be found to be affected with genetic diseases [2]. To perform PGD, embryos are created *in vitro* where the sperm and ovum

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are fertilised a petri dish, commonly known as in vitro fertilisation (IVF). Embryos produced via IVF will then be allowed to develop to three to five days after fertilisation before implantation process begins [3]. In PGD, the next step after fertilisation of embryos is the biopsy stage to screen for the existence of genetic disease or disorder in the embryos [4]. Only healthy embryos that are found not to have any genetic abnormalities will be chosen for implantation into the woman's uterus. PGD, thus, reduces the risks of producing children who will be affected with genetic diseases or abnormalities [5].

3.1.2. Gene Therapy

Some diseases are genetic in nature. Gene therapy, thus, works to treat or avoid the disease by addressing the principal genetic problem [6]. Rather than using medicine or other medical treatments, gene therapy paves the way for treating diseases by modifying a person's genetic make-up [6]. Previously, gene therapy functions in two ways: first, by adding a new gene into cells to treat the disease; or secondly, by inserting a copy of a gene that is good and healthy to replace the defective gene that instigates the disease [6]. For example, in the United Kingdom (UK), the first baby to have received gene therapy to cure a genetic disease called metachromatic leukodystrophy (MLD) was reported in February 2023 [7]. Gene therapy was used by removing the affected child's stem cells. The faulty gene that causes the disease are replaced and the treated cells are inserted in the patient's body [7].

Currently, a new method of gene therapy or also known as genome editing, has been introduced to replace the earlier methods. Genome editing can be achieved in three ways: first, by editing human zygote that results in the creation of genetically modified embryos; second, by altering the human germline cells that is the sperm or the oocyte; and third, by modifying the pluripotent stem cells that can grow into gametes and fertilised later [8]. An example of genome editing is a technique called CRISPR-Cas9 which has changed the approach of gene therapy. This method alters the existing DNA in the cell rather than introducing a new one [6]. In short, CRISPR-Cas9 is:

> *"a unique technology that enables geneticists and medical researchers to edit parts of the genome by removing, adding or altering sections of the DNA sequence. It is currently the simplest, most versatile and precise method of genetic manipulation and is therefore causing a buzz in the science world."* [9]

The use of CRISPR-CAS9 on germline cells such as the sperm, oocytes or early embryos, also called germline gene editing, raises ethical concerns that need to be scrutinised [10]. As such, it is essential to discover whether adequate laws or guidelines have been put in place to regulate these technologies.

3.2. The Law on PGD and Gene Therapy in Malaysia

At the time of writing this paper, assisted reproductive technologies (ART) are largely unregulated in Malaysia where there is currently, no law governing the practice. However, a law to regulated ART is said to be currently underway [11]. While this law is being prepared, the Ministry of Health Malaysia has issued an interim Guideline that is known the National Assisted Reproductive Technology (ART) Policy in 2021 ("the ART National Policy 2021") [11]. Earlier, several other guidelines have been formulated by the Malaysian Medical Council (MMC) and the Ministry of Health, Malaysia such as the MMC Guideline on Assisted Reproduction 003/2006 [12] and MMC Guideline on Medical Genetics and Genetic Services 010/2006 [13]. These Guidelines contains provisions concerning gene therapy and PGD. For example, section 14 of the MMC Guideline on Assisted Reproduction regulates the use of PGD by stating that:

> *"At present, it is best that PGD be used for only severe and life-threatening genetic diseases. It would be unethical to analyse and select the inherited characteristics of embryos (e.g. intelligence, height, hair and eye colour); any social of psychological characteristics or any other condition which is not associated with disability or a serious medical condition." [12]*

However, the definition or scope of "severe and life-threatening genetic diseases" mentioned in section 14 is not elaborated in the Guideline or elsewhere. Similarly, what should be accepted as a "serious medical condition" that warrants the use of PGD is also left to interpretation. The ART National Policy 2021 also contains a brief of provision on PGD which is described in the document as Pre-implantation Genetic Testing in section 3.1.1 [11]. Section 3.2.1 of the said Policy only contains a prohibition on sex selection of embryos for "social or personal reasons". Sex selection is nevertheless permitted in the said provision "if a particular sex predisposes to be a serious genetic condition e.g. haemophilia, Duchenne muscular dystrophy, fragile X syndrome, etc."

Malaysian laws are also silent on the potential introduction of gene therapy although its breakthrough is anticipated [14]. This is reflected in section 19 of the Malaysian Medical Council Guideline on Medical Genetics and Genetic Services 010/2006 [13] that recognises that: "Issues likely to present health professionals with ethical dilemmas are gene therapy and cloning." Later in 2009, the Medical Development

Division of the Ministry of Health of Malaysia has issued Guidelines for Stem Cell Research and Therapy (2009) [15] which also acknowledge the potential use of gene therapy. Section 2(e) of Guideline for Stem Cell Therapy [15] acknowledges that:

> *"Gene therapy to correct genetic disorder e.g. subacute combined immune deficiency disorders (SCID) and thalassaemia is still in developmental phase. The use of lentiviral shall be carried out in a P3 laboratory."*

Nonetheless, the 2021 National ART Policy [11] contains a provision which implies the possible prohibition of gene therapy. According to section 6.4.1, "Alteration of genetic structure if any cell while it forms part of an embryo is prohibited." It is uncertain as to whether this provision can be construed as an exclusion on the use of gene therapy as no specific mention is made on the technology unlike in the Guidelines for Stem Cell Research and Therapy (2009) [15]. The lacuna in the Malaysian law on the acceptability of gene therapy and PGD requires consideration of the ethical issues that these technologies bring. In what follows, some of the common concerns on both techniques are analysed.

3.3. The Issues

Although the methods in which both technologies work differ, they share several common ethical concerns. In this paper, two main ethical issues are chosen for analysis namely, the potential harm to the embryos and the child born (through the creation of a 'designer baby'). Additionally, the Islamic standpoint on both techniques is also explored.

3.3.1. Potential Harm on the Embryos

One of the critics advanced against embryonic testing using PGD is the potential destruction of embryos. To use PGD, multiple embryos are created *in vitro* which are then screened to detect the presence of unwanted traits such as genetic disorders or chromosomal abnormalities or even the sex of the embryos. Embryos found to have these undesired characteristics will have to be discarded or left to perish [16]. Hence, critics argue that PGD should not be allowed on the grounds of protecting the embryos [17].

On the other hand, germline gene editing or gene therapy has been hailed as a more acceptable process as the method allows for the modification of affected embryos which can then be implanted into the uterus. In other words, "By allowing a direct fix, embryos could be transferred that otherwise would have been discarded" [8]. There is a technical obstacle, however, in performing gene editing. Gene editing needs to be performed as early as with fertilisation or after fertilisation and before the first cell division [18]. PGD cannot be performed at this early stage and consequently, all embryos produced will have to undergo gene editing. Consequently:

> *"...when not all embryos are affected, one either has to neglect embryo testing and apply GGE 'blindly' at an early stage, thereby risking harming some otherwise suitable non-mutant embryos, or applying GGE later after mutant embryos were identified and thereby accepting a loss in efficacy owing to an increased risk of mosaicism. Both options create additional risks of embryos being damaged."* [8]

The objections on discarding embryos in PGD and genome editing on embryos is grounded on the moral and legal status of embryos. While it is accepted that there is no consensus on the moral status of embryos, the legal position in Malaysia needs to be ascertained. The law in Malaysia does not expressly protect *in vitro* embryos as evident in Chin Yoke Teng v William Ui Ye Mein *[2005] 2 MLJ 480* [19]. In this case, the High Court states at page 483 that: "And as far as I know 'human being' means a living human, and has never been interpreted to include the unborn child."

If the law does not accord legal personality to an unborn child inside the uterus, the same implication can be imposed on *in vitro* embryos which are not even implanted into the uterus. However, there are several available guidelines that safeguard the moral status of embryos as seen in the Malaysian Medical Council (MMC) Guideline on Assisted Reproduction 003/2006 [12]. Section 14 of which provides:

> *"As there is no worldwide agreement as to when human life begins or when it acquires moral significance, there is no agreement on the moral status of an embryo. Nor there is any agreement as to whether discarding an embryo with a genetic disorder, prior to implantation, is the equivalent of an abortion. At present, it is best that PGD be used for only severe and life-threatening genetic diseases."*

Section 15 of the said Guideline [12], further, provides protection on in vitro embryos by prohibiting research on embryos after 14 days from conception:

In summary, both PGD and gene therapy research requires embryos to be created and some destroyed. As such, further analysis is prompted due to the moral worth of the embryos. Even if the intervention on embryos can be justified, another issue has emerged on the potential

effects of both technologies on the child born.

3.3.2. Potential Harm to The Child Born: The 'Designer-Baby'

Genetic selection of children such as using PGD has been condemned for the fear of the creation of a 'designer baby.' King (1999: 181) [20], for example, laments that uncontrolled practice of PGD will lead the slippery slope to create what is called 'designer babies.'. He contends that there is a likelihood for parents to choose only the best traits in their future child. Children should not be viewed as a commodity but instead should be received 'unconditionally' as a gift from God to all parents [21]. The President's Council on Bioethics [22] expresses the view that children should not be 'selected' but instead are a gift to parents. In addition, King [23] further argues that selecting the characteristic of children turn the whole process of reproduction into a "another consumer experience."

Nonetheless, Robertson [24] argues that preconception selection of offspring need not necessarily pose a threat of harm to the child born as parents will often select for a positive traits or health of their child. This selection will produce a "healthier and happier child" who will have a promising future in life than children born with the undesired traits that parents have chosen against. This argument rings true in the case of PGD to select for embryos free from genetic diseases where healthy embryos are selected over those found to be affected with genetic diseases. Thus, only a healthy child is born and no other than that particularly due to the fact that PGD only allows for the selection of embryos. Weiss [25] surmises that there is no evidence to suggest that PGD leads to adverse clinical consequences on the child born from the technique and impacts parent-child relationship.

The concern on potential modification of children is, however, more plausible as gene therapy is on the horizon. As explained earlier, the advent of CRISPR-Cas9 genome editing technique has now paved the way for the modification of DNA in an embryo. Robertson [24] has long advances his stance on the acceptability of therapeutic and non-therapeutic genetic enhancement using germline gene therapy. According to Robertson [24], the aim of therapeutic germline gene therapy is to cure diseases and produce a healthy child. As such, if the technique can be proven to be safe and reliable, it cannot be opposed on the grounds of harm to the child as it allows a healthy child to be born. This child would not otherwise be born or would be born with a serious disease. A similar argument is advanced for non-therapeutic genetic enhancement where he argues that:

> *"Nontherapeutic genetic enhancement also aims to benefit the child by strengthening and reinforcing its positive characteristics. The aim is to better equip the child for life's perilous journey, and thus to assure that it will be happy and successful." (Robertson, 1996: 465) [24]*

Although Robertson [24] acknowledges the possibility that parents may use germline therapy to design children with their preferred attributes, he still believes that parents would do so for the benefit and well-being of their children. After all, "The fact that the child would have been just fine without the enhancement does not show that it will be harmed by this extra effort, any more than it would be harmed by extra tutoring or orthodontia" [24]. In addition, parents been known to make all sort of decisions on the future of their children. As Green [26] rightly stipulates that parents should be given the authority to decide on their child's future as parents are "both guardian and gardeners."

Moreover, parental legal rights to make medical decisions for their children has been long established. In most jurisdictions including Malaysia, consent for medical treatment for children below the age of 18 years is vested with the parents or legal guardian [27]. Section 2(a) of the Malaysian Child Act 2001 defines a child as a person below the age of 18. Accordingly, the Malaysian Medical Council Guideline on Consent for Treatment of Patients by Registered Medical Practitioner (n.d.) [28] stipulates that children below the age of 18 does not generally have the capacity to consent and therefore, consent should be obtained from a parent or legal guardian (section 6).

Hence, as argued elsewhere, the supremacy of parental autonomy in deciding on matters concerning their children should only be limited when there is proof of harm such as a threat to the child's life. In other circumstances, parental autonomy should not be interfered with by the State [29]. Nonetheless, germline genome editing invites further scrutiny on the issue of the lack of consent from future generations whose genes have been altered [30]. Any alterations to the genes by genome editing will possibly affect future generations who have not consented to such a treatment. Coller [31] rightly argues that these changes may be less problematic when used to prevent the transmission of serious diseases. But, as this technology advances, the possibility of it being used to boost human abilities or to introduce new DNA sequences cannot be dismissed. Thus, the need to pass law or ethical guidelines on genome editing cannot be undermined [31].

3.4. The Islamic Perspective

PGD on the grounds of avoiding the birth of children with genetic diseases have been ruled as

permissible by the *Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia* on 22 February 2005 [32]. According to the Fatwa, it is permissible to conduct research on pre-embryos in order to detect the presence of genetic diseases and only healthy embryos can be implanted within a valid marriage.

However, as Islam only allows the use of IVF for married couples only, it follows that PGD can only be accessed by married couples as the use of PGD requires fertilisation of embryos using IVF. This fatwa on the permissibility of IVF in Islam for married couples only has been decided during the 5th *Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia* on 16-17 November 1982 and the 6th *Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia* on 10 October 1983 [32].

The Fatwa committee has also deliberated on the issue of modifying pre-embryos which can be associated with gene therapy. According to the fatwa, genetic engineering on pre-embryos that involves modification on the natural traits such as hair colour, IQ and including sex is prohibited. Sex selection is only permissible to avoid the transmission of genetic diseases that can lead to death. In summary, genetic modification of pre-embryos for non-therapeutic reasons are strictly prohibited in Islam.

4. Conclusion

Technological advances in medicine is usually applauded for the benefits it confers on human beings. It is conceded that both PGD and gene therapy offer huge benefits to humans particularly in ensuring the birth of children without genetic diseases. However, they also raise possible risks of harm to the embryos and the child born. While PGD is now available in this country, gene therapy is still underway. As such, it is timely for a specific law to be put in place in Malaysia in order to mitigate these risks. The introduction of this law will serve as a protection to society by resolving the ethical conundrums that they are likely to face from the use of modern medical technologies such as gene therapy and PGD.

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