In vitro fertilization as an option for couples with genetic disorders

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Errors in human DNA may cause genetic disorders. Technological developments have raised hopes for reducing the risks of genetic inheritance among married couples who have a history of such disorders. Among the developments in reproductive health technology that reduce those risks is the in vitro fertilization (IVF) process. This review aimed to describe the current strategies using IVF and preimplantation genetic testing (PGT), which would be effective for couples with genetic disorders to have healthy offspring. The literature review included full-text, open-access research articles from ScienceDirect, PubMed, and Google Scholar that were published between 2013 and 2023, with 65 articles obtained from various journals. The keywords were “in vitro fertilization,” “reproductive genetic disorders,” “PGT-A,” “PGT-M,” “PGT-SR,” and “oocyte donor.” A total of 46 articles were selected as the most relevant to the review topic, and the results show that the IVF process can be an option for couples with a history of genetic disorders. Several additional procedures can be performed following IVF, such as oocyte donation and PGT, to help couples who want to have offspring without transmitting their genetic disorders. IVF can be an option for couples who have or carry genetic disorders. With IVF, couples can undertake several procedures such as oocyte donation and PGT for aneuploidy, monogenic disorders, or structural rearrangement.

Keywords: Genetic diseases, inborn; In vitro fertilization; Oocyte donors; Preimplantation genetic testing

Introduction

An error in human DNA, such as a single base mutation, single or multiple gene defects, or a change in the number of chromosomes, may cause a medical condition known as a genetic disorder. Such disorders may affect development in various ways. The three main categories are single-gene, chromosomal, and complex disorders [1].

When a genetic disorder is diagnosed in a family, it is likely that the family members and their children would want to know about the condition’s heritability. Because many factors may influence the chances of inheriting the disorder, it may be difficult to predict. After receiving genetic counseling, the couple will likely want to try again to conceive, despite their advanced age. Infertility management requires comprehensive and thorough approaches [2]. In a family with a history of genetic disorders, it is crucial to be aware of the disorders and the possible risks associated with childbirth. Along with technological developments, access to healthcare services has increased for families with a history of genetic disorders, especially regarding efforts to reduce the risk of transmitting genetic disorders to their children and to give them a better quality of life.

In the field of reproductive health, in vitro fertilization (IVF) is a technique that can help couples to have children. It involves joining mature oocytes and spermatozoa outside the human body [3,4]. Initially, IVF was applied to help infertile couples to produce offspring. As public knowledge of reproductive technology develops, members of the public desire to have healthy children. The role of IVF has been extended to help couples with a history of genetic disorders have healthy children through optional measures. The current paper aimed to delineate the contemporary IVF options for couples, especially those with a history of genetic disorders, to have healthy children.
Methods

For this literature review, we searched for articles containing the topic of IVF options for people with reproductive genetic disorders. The inclusion criteria used were full-text, open-access research articles from ScienceDirect, PubMed, and Google Scholar which were published between 2013 and 2023. We chose 46 articles that passed the inclusion criteria through the following stages: database search (n=250) with the keywords “in vitro fertilization,” “reproductive genetic disorders,” “PGT-A,” “PGT-M,” “PGT-SR,” and “oocyte donor”; screening of articles by title (n=65); and screening of articles by abstract and type of study (n=46).

Results and discussion

IVF is an assisted reproductive technology that is typically used for couples with histories of primary and secondary infertility. For couples with various causative factors or a family history of genetic disorders, IVF may offer help because each step of the process of conception is controlled. Patients with genetic disorders may be able to benefit from IVF through oocyte donation and preimplantation genetic testing (PGT).

The IVF process begins with controlled ovarian hyperstimulation (COH) and progresses through egg retrieval, fusion of egg cells with the sperm, embryo development, and embryo transfer. COH is accomplished through administering a combination of gonadotropin and gonadotropin antagonist, along with human chorionic gonadotropin. Following a series of ovarian stimulation procedures, the next steps are egg retrieval, sperm preparation, fertilization by intracytoplasmic sperm injection (ICSI), and monitoring of embryonic development. Embryonic development is monitored during IVF until the embryos cleave on the third or fifth day [5].

Oocyte donation

In 1983, oocyte donation was first performed in Austria. Since then, it has become part of assisted reproductive technology. Oocyte donation may be offered to women with a genetic abnormality to prevent their children from inheriting the associated disorder, such as Huntington's disease or thalassemia [6-8]. Donor oocytes are paired with sperm from the patient’s partner [9].

The indications for using donor oocytes include hypergonadotropic hypogonadism, advanced age, a history of diminished ovarian reserves, and genetic disorders. The stringent selection criteria for oocyte donors include age, medical and genetic history, good mental health, and having received genetic counseling [10].

The oocyte donor is given drugs to suppress natural hormone production. Hormone injections are administered for COH, and the results are evaluated through a transvaginal ultrasound examination. The next step is the selection of oocyte cells, which can then be frozen or directly fertilized with sperm [6]. After the fertilization process, the developing embryo is transferred into the recipient’s endometrium.

Although oocyte donation can be an option for helping patients who want to have children without transmitting their genetic disorders, the procedure raises ethical issues because of the link between oocyte donors and commercialization, and the possibility of the exploitation of women [11]. Several countries, such as Indonesia, do not allow couples to use oocyte donation [12]. Other countries, such as Costa Rica and Italy, prohibit reproduction through gamete donation [13].

Preimplantation genetic testing

PGT is a procedure to analyze embryos genetically for couples who have a high risk of passing genetic disorders to their children. It requires IVF so that the procedures may occur in sequence. Fertilization through ICSI is preferred for PGT so that the risk of contamination is limited from residual cumulus cells or sperm cell remnants in the zona pellucida [14].

Common indicators for using PGT currently include myotonic dystrophy type 1, hemoglobinopathies such as thalassemia and sickle cell anemia, cystic fibrosis, late-onset neurodegenerative disorders such as Huntington’s disease, hereditary cancer syndromes such as breast and ovarian cancer (BRCA1 and BRCA2), and structural chromosomal anomalies [15,16]. Recurrent miscarriage, implantation failure, male factor infertility, advanced maternal and paternal ages, and parental genetic abnormalities such as sex chromosome mosaicism are also indications for PGT [17,18].

The three types of PGT currently in use are PGT for detecting aneuploidy (PGT-A), PGT for monogenic disorders (PGT-M), and PGT for structural rearrangements (PGT-SR). PGT-M and PGT-SR are also known as preimplantation genetic diagnosis (PGD) methods [19]. These types of PGT differ in practice, beginning with initial referral through the IVF program and continuing with follow-up on pregnancy, birth, and children, as described by the European Society of Human Reproduction and Embryology (ESHRE) PGT consortium (Figure 1) [20].

PGT for detecting aneuploidy

PGT-A is a genetic test used before implantation to identify aneuploid embryos. Humans have 46 chromosomes, but in aneuploidy conditions, the cells have an incorrect number of chromosomes, such as 45 or 47 [21]. The goals of PGT-A during the IVF process are to improve the conditions for pregnancy, reduce the risk of chromosomal abnormal pregnancies, and reduce the risk of miscarriage. PGT-A is also used increasingly to reduce the risk of inheriting certain diseases [17,22]. For infertility, to improve the odds of pregnancy or
reduce the odds of miscarriage, PGT-A is used to select euploid embryos in cases of recurrent implantation failure or advanced maternal age. Many couples choose PGT-A because they want to avoid an abortion if a fetus would show chromosomal abnormalities and disabilities as it develops into a child [23].

PGT-A consists of three main stages—namely, embryo biopsy, chromosomal screening, and embryo transfer, and is generally preceded by the IVF process. The patient undergoes a series of ovarian stimulation, egg collection, sperm preparation, and ICSI. The embryo biopsy process can be performed on oocytes' polar bodies, embryos in the 6–8 cell cleavage stage, or embryos in the blastocyst phase (Figure 2) [24]. In a polar body biopsy, the first polar body is biopsied on day 0, and the second polar body is biopsied on the first day after visible fertilization. Subsequent biopsies can be performed at the 6–8 cell embryonic cleavage stage, from which 1 to 2 cells are taken after the zona has been thinned with acid Tyrode’s solution or a laser. As for blastocyst biopsy, the zona can be perforated on day 3 or day 5, which allows some trophectoderm to emerge through the hole on day 5, after which about five trophectoderm cells are taken or cut [25]. The most commonly used technique is blastocyst biopsy because the blastocyst contains numerous cells yet is still embryonic, making it more amenable to genetic evaluation and less susceptible to damage [20].

Chromosomal screening uses comprehensive screening technology to analyze chromosomes [24]. One common technique, next-generation sequencing (NGS), determines the number of chromosomes in each embryo biopsy, distinguishes between normal (euploid) embryos and aneuploid embryos, and enables detection of chromosomal mosaicism at 20%–80% accuracy [26,27]. Mosaic embryos contain both euploid and aneuploid cells, as determined by preimplantation genetic analysis.

The chromosomes are examined to make sure they are not aneuploid before the embryo transfer procedure is attempted. In addition, euploid embryos can be frozen if they are to be reserved for future use. For mosaic embryos, this requires good management. PGT-A faces a critical challenge in managing mosaicism. Embryonic mosaicism originates from post-zygotic chromosome segregation errors caused by mitotic non-disjunction, anaphase lag, chromosome some deletion, or duplication [28]. If there are no euploid embryos and only mosaic embryos are available, then it is more advisable to transfer or freeze single embryos, prioritized by the level and type of their mosaic traits [29,30]. According to a study that evaluated 1,000 mosaic embryos, the prioritization scheme applies to all embryos regarding their morphology and mosaic attributes [31].

PGT-A has the advantage of increasing the chances of implantation and pregnancy while decreasing the risk of miscarriage. PGT-A in IVF transfers the healthiest embryos to improve clinical pregnancy and birth outcomes [24]. According to a study by He et al. [32], the “clinical pregnancy and birth rates in the PGT-A group were higher than in the IVF-conventional group.” That is, the PGT-A group of patients aged ≥40 years had a significantly higher pregnancy success rate than those in the non-PGT-A group (Figure 3) [33].

Although PGT-A has various advantages, it also has several weaknesses. The presence of arrested cells and debris in the zona pellucida of blastocysts suggests a self-correction mechanism during early embryonic development [34]. The observed self-correcting ability of
human embryos poses a challenge to many invasive and non-invasive PGT-A procedures at the blastocyst stage, resulting in the identification of cell-free DNA from human embryos. This results in a high rate of false positives [35]. Biopsy procedures from the cleavage stage to the blastocyst phase, along with vitrification techniques, have improved PGT-A’s reproductive outcomes. However, the biopsy process may damage an embryo [36].

Among PGT-A’s deficiencies is the risk of misdiagnosis by indicating genetic results different from the correct genetic code of the sample under analysis. Possible risks include human errors such as incorrect labeling or contamination, errors in choosing methods, and errors in the use of diagnostic techniques [18]. In addition, PGT-A requires a higher cost than conventional IVF. The average cost for patients undergoing PGT-A is 9.23% higher [32]. Several patient groups still reject the PGT-A. Many couples refuse to consider PGT-A due to their religious values [17].

PGT for monogenic disorders

PGT-M is used in cases of single-gene disorders caused by mutations in specific regions of a single gene. When such disorders are heritable, they are likely to affect the children of an individual with the disorder. Cystic fibrosis, sickle cell anemia, muscular dystrophy, fragile-X syndrome, and spinal muscular atrophy type 3 are examples of monogenic disorders [37].

PGT-M is known as PGD for a single gene. PGD, which involves extracting cells from an embryo suspected of having a genetic disorder, was first performed on human embryos more than 26 years ago [38]. PGT-M is performed to diagnose specific disorders in embryos with specific risks of heritability [39]. This process involves assisted reproductive technology through IVF. In the ESHRE PGD Consortium and large United States centers, PGT-M cases for non-disclosure account for 5%–10% of all single-gene disorders [38].

The PGT-M stage involves the process of IVF starting from gamete preparation and fertilization until the embryo stage is reached. After an embryo is obtained, among the techniques used for PGT-M are linkage analysis, sequencing, karyomapping, and NGS. PGT-M may also involve PGT-A because of its procedures regarding cell biopsy and chromosomal analysis. The characteristics, applications, and limitations of each method are presented in Table 1 [37].

PGT-M can detect >99% of inherited single-gene disorders. PGT-M can also identify both affected and unaffected embryos with >98% accuracy [40]. The combination of PGT-A and PGT-M may be used to diagnose and screen embryos at the same time. When both partners are asymptomatic carriers of a mutation, one partner has a genetic disorder, and both partners show evidence of abnormality, this method is selected [37].

The results of PGT-M are improved when it is followed by PGT-A. Unsal et al. [41] found that “PGT-M and 24 chromosome testing in 44 patients revealed that 49% of the embryos examined were euploid and 64% of pregnancies were achieved through PGT-M, followed by PGT-A.” Nonetheless, PGT-A before PGT-M is the most cost-effective approach for X-linked, autosomal recessive gene disorders, and it can
avoid the intensive laboratory testing required by genetic laborato-
ries [42].

**PGT for structural rearrangements**

PGT-SR identifies embryos with the correct (balanced and normal) amount of genetic material, as well as embryos with excess or deficient amounts of genetic material due to translocations or rearrange-
ments (unbalanced) [43]. PGT-SR is more effective than traditional prenatal diagnostic methods in helping couples achieve an unevent-
ful pregnancy and deliver a child without unbalanced translocation.

After IVF, PGT-SR is available to evaluate human embryos from parents with the most common type of structural rearrangement, a Robertsonian or reciprocal translocation [44]. The priority in using PGT-SR is to give couples with chromosomal rearrangements a similar opportunity to have a child with a normal karyotype [45]. This test applies fluorescence in situ hybridization (FISH), microarray comparative genome hybridization (aCGH), and NGS [46]. NGS had the highest birth outcome of these three techniques (73.7%) when com-
pared to FISH and aCGH [44].

**Ethical issues regarding the use of PGT**

Although IVF followed by the PGT process can help couples have genetically normal children, it may provoke ethical problems such as embryo selection, sex selection, and so-called designer babies [47]. Selecting the best embryos for clinical use can increase the potential for embryos to be discarded upon donation for research. This raises an ethical issue related to the medical oath and the terms in the In-
donesian Code of Medical Ethics or Kode Etik Kedokteran Indonesia (KODEKI), which states that humans are considered to be alive from the moment of conception. In addition, the selection of embryos has ethical issues related to religious norms. Regarding sex selection, the results of PGT reveal an embryo’s sex as well as any X-linked diseases that may be inherited. Some couples may undertake PGT primarily to find out the sex of their child and then select embryos based on that information. Furthermore, PGT has the potential to develop into modern eugenics, in which children are designed according to the wishes of the couple who undergo testing. Because of these ethical issues that might arise from IVF with PGT, it is necessary to regulate the examination of genetic disorders.

**Conclusion**

Based on the literature review above, IVF may be an option for couples who have or carry genetic disorders. IVF enables a couple to undertake several alternative actions, such as oocyte donation and PGT (PGT-A, PGT-M, PGT-SR) through IVF. As a result of PGT, couples with genetic disorders are expected to be able to have genetically normal children. However, in practice, couples who choose one of the four alternatives above should still pay attention to ethics, norms, and cost-effectiveness.

**Conflict of interest**

No potential conflict of interest relevant to this article was report-
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