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The relationship between genetic polymorphisms and *in vitro* Fertilization (IVF) in women: A review

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Abstract

While infertility is a global problem that affects millions, *in vitro* Fertilization (IVF) provides hope for many. Despite technology-driven advancements in IVF, its success rates are still, to some extent, erratic due to a lack of profound knowledge about biological variables regulating fertility dynamics. Recent scientific findings focused on genetics, especially genetic polymorphisms, have underlined the great importance of being able to forecast IVF outcomes. In this literature review, the relationship between genetic predisposition in female infertility via case-control studies applying Single Nucleotide Polymorphism (SNP) analysis of ovarian reserve genes that control ovary tissue, plus hormone regulation and embryo cleavage, was reviewed. Chromosomal anomalies, including genetic disorders (e.g., Turner syndrome), are also reviewed with respect to their effects on IVF clinical outcomes due to their implications for implantation and miscarriage rates. This review highlights the promise of genetic screening in giving rise to personalized treatment options in reproductive medicine through a survey of studies on gene mutations and chromosomal aberrations. The observation implies that adding genetic profiling to routine IVF programs might increase the chance of success, helping personalized reproductive care.

Keywords: Genetic polymorphisms, chromosomal variations, genetic disorders, IVF outcomes, genetic screening

Introduction

In vitro Fertilization (IVF) is a common kind of Assisted Reproductive Technology (ART). IVF has come a long way since successfully using it for the first time in 1978 and offers hope to couples all over the world who are struggling with fertility when other treatments have failed (Zhao *et al.*, 2011) ^[1]. It consists of the removal of oocytes from a woman's ovaries, fertilization with sperm *in vitro*, and the transfer of an embryo to the uterus once it is formed. Nevertheless, despite these technological and scientific advances, there is wide variability in the success rate of IVF that can be influenced by multiple factors, including biological, environmental and genetic aspects (Iketubosin, 2018) ^[2].

Since then, the importance of genetics as a key player in fertility and IVF success has been implicated to an increasing extent. It has been suggested that the inheritance of specific genes or genetic variations of Single Nucleotide Polymorphisms (SNPs) may influence different types of reproductive processes such as ovarian response, oocyte and embryo production to quality issues, and implantation stage, but not necessarily disorders with major effects (Tahmasbpour *et al.*, 2014) ^[4]. The interaction between genetics and IVF results has given rise to a saturated branch of research that seeks exactly what molecular constituents could serve as reliable prognosis markers or siblings-preparation tools for achieving *in vitro* Fertilization (IVF) treatment success rates (Karimian *et al.*, 2021) ^[3].

Significant knowledge provides valuable insights into how various genetic-related factors interact to impact IVF and sheds light on the intricate biological pathways underlying reproductive success. Each of these genes contributes a distinct step along this path, from ovarian function to hormonal regulation. As an example, polymorphisms in both Follicle-Stimulating Hormone Receptor (FSHR) and anti-Müllerian hormone receptors have been linked to variability of ovarian reserve and response to hormonal stimulation during IVF

cycles (Persani *et al.*, 2014) ^[6]. However, advances in genetic research are paving the way for personalized medicine applications in reproductive health, that may adapt treatments to unique genetic profiles of patients, enhancing outcomes (De Pascali *et al.*, 2018) ^[5].

Besides gene polymorphisms, chromosomal abnormalities are another genetic factor that could largely influence the success rate of *in vitro* Fertilization (IVF). It is well accepted that women carrying a chromosomal abnormality, such as a reciprocal translocation or chromosomal mosaicism are at greater risk of implantation failure or miscarriage (Viotti, 2020) ^[7]. This has been shown by studies using preimplantation genetic testing for aneuploidies (PGT-A), which demonstrate that the identification of chromosomal variation before embryo transfer can increase IVF success rates through selection of embryos with a normal chromosomal complement (Harris *et al.*, 2021) ^[8].

Literature review

The role of genetic background in female infertility

Because genes control ovarian mechanisms, hormone production, and embryo development, the genetic background is an important determinant of a person's fertility. Several genetic traits are inherited, and they impact fertility where some gene variants contribute to follicle maturation, hormone secretion and, in general, reproductive cyclical attainment (Chen *et al.*, 2023) ^[9]. An example is mutations affecting genes controlling ovarian reserve, such as the Anti-Müllerian Hormone (AMH) and its receptor gene AMHR2 which have been associated with a decrease in ovarian function of premature menopause ovaries failure. These gene variants lead to reduced follicular reserves, consequently affecting the reproductive lifespan and fertility in human females (Bedenk *et al.*, 2020) ^[10].

Repetitive polymorphisms in reproductive hormone-related genes also strongly affect female infertility. As an example, polymorphism of the FSHR (follicle-stimulating hormone receptor) gene modifies the ovarian response to stimulation. One such example is the FSHR Asn680Ser variant, which has been associated with a lessened response to gonadotropin therapy used in ovulation induction for IVF (Ricetti *et al.*, 2017; Binder *et al.*, 2012) ^[11, 12]. Decreased ovulatory response will ultimately lower the egg yield, and consequently influence the possibility of fertilization and pregnancy success, therefore reflecting a reproductive outcome for this gene (Cheung *et al.*, 2019) ^[13].

Another important genetic factor is the Luteinizing Hormone Receptor (LHR) gene, which in female patients with infertility has been shown to be related to low plasma anti-Müllerian hormone concentrations (Di Clemente *et al.*, 2021) ^[14]. Luteinizing Hormone Receptor (LHR) gene mediates the effects of Luteinizing Hormone (LH) on ovulation and steroidogenesis in the ovary. Perhaps most relevant to the effect of LH on stimulatory response. (Narayan, 2015) ^[15]. Many of these polymorphisms have been found to be associated with diseases such as Polycystic Ovary Syndrome (PCOS), among other causes, or, in some cases, the primary cause of infertility in women (Oduwole *et al.*, 2021) ^[16].

In addition to hormone-related genes, variants in embryo development-associated genes affect fertility. Insulin-like Growth Factor (IGF) could regulate the activity of the embryo. Studies have shown that certain gene

polymorphisms may interfere with those mechanisms and result in decreased embryo implantation potential leading to a higher rate of implantation failure in the case of assisted reproductive techniques (Javadmanesh, 2013) ^[17]. The genetic control of embryo development proves that different reproductive stages are environmentally and genetically affected (Dolinoy *et al.*, 2007) ^[18].

The impact of genetic polymorphisms on IVF clinical outcomes:

Clinical results of *in vitro* Fertilization (IVF) are substantially influenced by genetic variations, especially Single Nucleotide Polymorphisms (SNPs). Several IVF phases have been demonstrated to be impacted by SNPs in genes linked to ovarian response, embryo quality, and endometrial receptivity. For example, polymorphisms in the Follicle-Stimulating Hormone Receptor (FSHR) gene including the Asn680Ser polymorphism have been associated to changes in ovarian response during stimulation. Women with certain FSHR genotypes show a reduced response to gonadotropin treatment, which results in less retrieved oocytes, therefore reducing the possibilities of successful fertilization and pregnancy (Čuš *et al.*, 2019; Mohiyiddeen *et al.*, 2013) ^[19, 20].

Likewise, Variations in the Estrogen Receptor (ESR1) gene have been linked to affective outcome of IVF. Maintaining pregnancy and getting the endometrium ready for implantation depend on estrogen in great part. Studies have linked certain ESR1 gene variants such as XbaI and PvuII polymorphisms to changed endometrial receptivity, therefore influencing perhaps implantation rates and pregnancy outcomes. Reduced conception rates among women with these ESR1 mutations highlight the gene's importance in IVF cycle reproduction (Altmäe *et al.*, 2007; De Mattos *et al.*, 2014) ^[21, 22].

Because of its impact on ovarian reserve and responsiveness, the Anti-Müllerian Hormone (AMH) and its receptor (AMHR2) also are crucial in IVF results. Commonly employed as a measure of ovarian reserve, AMH levels are linked to several AMHR2 gene mutations including the -482A>G variation, which lowers AMH levels and reduces ovarian responsiveness to stimulation. Women with these AMHR2 polymorphisms therefore typically have less accessible oocytes and may need more gonadotropin dosages, thereby influencing the general efficiency and success rates of IVF (Peluso *et al.*, 2014) ^[23].

Moreover affecting embryo quality and viability are genetic differences. For example, aberrant methylation patterns due to mutations in the Methylenetetrahydrofolate Reductase (MTHFR) gene, which is important in folate metabolism, can cause disturbance of embryo development. Variants include MTHFR C677T have been linked to a higher incidence of embryonic chromosomal abnormalities and implantation failure. This link between MTHFR polymorphisms and embryo quality points to genetic screening's potential to assist in the identification of couples who could have poor IVF results (Enciso *et al.*, 2016) ^[61].

Polymorphisms in the Progesterone Receptor (PGR) gene highlight even another way that genetic differences affect IVF results. Endometrial receptivity and embryo implantation depend on progesterone, so certain PGR variations have been related to variations in implantation success. Research on the PGR gene's polymorphism show that women with this variation might have reduced implantation and pregnancy rates during IVF, therefore

underlining the gene's role in successful embryo transfer (Da Silva *et al.*, 2018) ^[25].

Influence of chromosomal variations on IVF outcomes

IVF results are substantially influenced by chromosomal changes including structural rearrangements and numerical anomalies, which affect elements like embryo quality, implantation success, and miscarriage rates. Commonly seen in embryos from older women, chromosomal abnormalities where embryos have an aberrant number of chromosomes are associated to increased odds of IVF failure and early pregnancy loss. Chromosomal analysis is a useful method in evaluating embryo viability as aneuploid embryos typically fail to implant or cause miscarriage when implantation takes place (Viotti, 2020) ^[7].

A form of chromosomal structural disorder, reciprocal translocations arise when parts of two chromosomes exchange sites without any genetic material lost or gained. Although carriers of balanced translocations may be phenotypically normal, their gametes may have imbalanced chromosomal complements, which may cause implantation failure or recurrent miscarriage and hence cause reproductive difficulties. Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) may help detect embryos with balanced chromosomes, therefore enhancing the selection process for viable embryos and raising IVF success rates for these patients (Ogur *et al.*, 2020; Griffin & Ogur, 2023) ^[27, 28].

Mosaicism, in which an embryo combines cells with various chromosomal makeup, is another often occurring chromosomal problem influencing IVF results (Watt, 2019) ^[29]. Preimplantation genetic testing for aneuploidies (PGT-A) reveals mosaic embryos, which may still result in viable pregnancies but depending on the degree and kind of mosaicism the results differ. While high-level mosaic embryos frequently have inferior implantation success and greater miscarriage rates, research has revealed that low-level mosaic embryos have similar implantation rates to euploid (normal chromosomal makeup). Thus, correct evaluation of mosaicism by genetic testing may direct embryo selection and enhance clinical results in IVF (Lee, *et al.*, 2020) ^[30].

Furthermore contributing to fertility problems and influencing the outcome of assisted reproductive therapies are sex chromosomal abnormalities such Turner syndrome (45,X) and Klinefelter syndrome (47,XXY). Usually needing donor oocytes, women with Turner syndrome have decreased ovarian reserve and have difficulty with IVF. Men with Klinefelter syndrome, on the other hand, might have low sperm count or azoospermia, which calls for sophisticated reproductive technologies like IVF along with Testicular Sperm Extraction (TESE) (Rogol, 2023) ^[31].

By choosing embryos with a normal chromosomal makeup, Preimplantation Genetic Testing (PGT) for chromosomal abnormalities helps doctors enhance IVF results, therefore increasing the likelihood of successful implantation and lowering the miscarriage rates. Particularly for patients with known chromosomal defects or those suffering recurrent pregnancy loss, this method emphasizes the need of chromosomal screening in improving IVF success (Cheng, 2023) ^[9].

Influence of chromosomal variations on IVF outcomes

Major determinant of the clinical results of *in vitro* Fertilization (IVF) are chromosomal abnormalities, especially aneuploidies and structural rearrangements. Common in human embryos, aneuploidy defined as an aberrant chromosome count highly affects implantation rates

and pregnancy outcomes (Daughtry, & Chavez, 2016) ^[33]. Research indicates that aneuploid embryos especially those from women of advanced mother age are more likely to fail implantation or cause miscarriage should implantation take place. The great frequency of aneuploidy in embryos emphasizes the need of preimplantation genetic testing for aneuploidy (PGT-A), which may screen for embryos with a normal chromosomal complement and increase IVF success rates (Anderson *et al.*, 2020) ^[34].

Also very important for IVF results are structural rearrangements include reciprocal and Robertsonian translocations (Verdoni *et al.*, 2021) ^[35]. Although they have normal phenotypes, those with balanced translocations are prone to generate imbalanced gametes, which raises the likelihood of early pregnancy loss and implantation failure. Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR) has become a useful tool in identifying embryos with balanced chromosome structures, so enabling carriers of translocations to choose viable embryos for transfer and so greatly improving clinical outcomes (Boynukalin *et al.*, 2021) ^[36].

IVF results are further complicated by mosaicism where an embryo has a mix of cells with varying chromosomal makeup. Although the degree and kind of mosaicism will determine whether or not mosaic embryos found by sophisticated methods in preimplantation genetic testing have the chance for healthy pregnancies. While high-level mosaicism is linked with lower implantation rates and a greater probability of miscarriage, low-level mosaic embryos have implantation rates equivalent to those of euploid embryos. Mosaicism evaluation has therefore become essential for embryo selection as it enables doctors to improve their strategy to optimize IVF success (van Echten-Arends *et al.*, 2011) ^[37].

Some sex chromosomal defects, including Klinefelter syndrome (47,XXY) and Turner syndrome (45,X), can affect fertility results and call for specific reproductive treatments (Acién, & Acién, 2020) ^[38]. While men with Klinefelter syndrome often show with reduced sperm count or azoospermia, necessitating procedures like Testicular Sperm Extraction (TESE) combined with IVF, women with Turner syndrome typically show a reduced ovarian reserve and may need donor oocytes for successful conception. These chromosomal abnormalities highlight the need of chromosomal screening in determining the most appropriate treatments for impacted people and evaluating reproductive issues (Achermann *et al.*, 2021) ^[39].

Improving IVF success rates has shown mostly dependent on the incorporation of chromosomal screening for aneuploidies and structural rearrangements (PGT-A and PGT-SR). Choosing embryos with a normal chromosomal makeup helps doctor's lower miscarriage rates and raise the possibility of a successful implantation, therefore improving the odds of a pregnancy. Particularly for patients with recurrent pregnancy loss or known chromosomal abnormalities, this strategy shows the important function of genetic screening in reproductive medicine (Morales, 2024) ^[40].

Genetic disorders in infertile women

Affecting a spectrum of reproductive processes from ovarian development to hormone control, genetic abnormalities play a major role in female infertility. Among the most often investigated genetic diseases connected to

infertility is Polycystic Ovary Syndrome (PCOS), a complicated ailment marked by ovarian malfunction, hormone abnormalities, and irregular menstrual cycles (Legro & Strauss, 2002) ^[41]. Studies show that genetic predispositions specific genes such as those linked to insulin resistance (e.g., INSR) and androgen metabolism (e.g., CYP11A1) commonly shape PCOS development. PCOS is among the main causes of infertility among women as these genetic elements produce reproductive hormone abnormalities that affect ovulation (Piri-Gharaghie, 2021) ^[42].

Another hereditary condition linked to infertility is early ovarian insufficiency, also referred to as premature ovarian failure. Early depletion of ovarian follicles seen by women with POI causes menopause-like symptoms well before the usual age (Sharma *et al.*, 2023) ^[43]. Pathogenesis of POI has been linked to genetic elements including mutations in the FMR1 gene and other genes engaged in ovarian activity (e.g., BMP15). Accelerated follicular atresia and altered ovarian function brought on by these abnormalities lower reproductive potential and complicate natural or aided technique of conception (Rossetti *et al.*, 2017) ^[44].

Also significantly affects women's fertility Turner syndrome, a chromosomal condition marked by either partial or total lack of one X chromosome (45,X karyotype) (Fukami, 2023) ^[45]. Most women with Turner syndrome have ovarian dysgenesis, which drastically lowers ovarian reserve or often causes no functional ovarian tissue at all. Affected people have poor rates of spontaneous conception and often need assisted reproductive technologies due to a genetic anomaly; successful pregnancies depend mostly on donor eggs (Labrosse & Grynberg, 2022) ^[46].

Though mostly recognized as a gynecological disorder, endometriosis also has genetic roots related to infertility. Variations in the WNT4 and GREB1 genes are linked to higher endometriosis risk, which influences fertility by itself (Lalami *et al.*, 2021) ^[47]. These genetic elements help endometrial-like tissue outside the uterus develop abnormally, which causes inflammation and scarring that might interfere with ovulation, fertilisation, and embryo implantation, therefore resulting in infertility in the afflicted women (Cardoso *et al.*, 2020) ^[48].

Additionally linked to infertility is Kallmann syndrome, a hereditary condition that reduces reproductive hormone signaling by abnormalities in genes including KAL1 and FGFR1 (Kim, 2015) ^[49]. Lack of gonadotropin-releasing hormone (GnRH) production characterizes this disorder, which results in inadequate stimulation of the ovaries and no menstrual periods in women. Without appropriate GnRH signaling, ovarian function is reduced, leading to anovulation and infertility usually requiring hormone replacement treatment or assisted reproductive technologies for conception (Maggi *et al.*, 2016) ^[50].

Turner syndrome

A 45,X karyotype in afflicted people results from a partial or whole absence of one of the X chromosomes, defining the hereditary condition known as Turner Syndrome (TS). It affects reproductive health profoundly and happens in around 1 in 2,500 live female births. Usually experiencing ovarian dysgenesis, women with Turner syndrome either have a greatly decreased ovarian reserve or, in many instances, no functioning ovarian follicles. In most afflicted people, this chromosomal abnormality causes early ovarian

failure and infertility so, natural conception is difficult and sometimes calls for assisted reproductive technologies for pregnancy (Lamanna *et al.*, 2022) ^[51].

Although many women with Turner Syndrome have anomalies in the reproductive system, including shorter uterine length and a greater risk of anatomical deformities, the reproductive consequences of TS go beyond ovarian failure (White, 2014) ^[52]. These anatomical problems as well as ovarian insufficiency help to produce low fertility results. Studies show that only a tiny percentage of Turner syndrome sufferers have spontaneous pregnancies; many of them need oocyte donation to result in successful conception (Karnis *et al.*, 2003) ^[53]. Although patients still run higher risks during pregnancy, like hypertension and aortic problems, assisted reproductive technologies especially IVF utilizing donor oocytes have improved the odds of conception for women with TS (Cameron *et al.*, 2024) ^[54].

Apart from the physical difficulties related with infertility, women with Turner syndrome also run more danger during pregnancy. Studies have shown that structural cardiac problems common in TS provide major concerns about cardiovascular consequences including aortic dissection and rupture. For TS patients thinking about pregnancy, preconcept evaluations including cardiac imaging are crucial to evaluate their risk of problems and direct appropriate treatment planning. Women with TS are more likely to have disorders like preeclampsia and gestational hypertension, both of which may impair IVF and pregnancy outcomes, so cardiovascular monitoring throughout pregnancy is also very important (Oktay *et al.*, 2016) ^[56].

Although developments in reproductive treatments provide optimism, Turner syndrome still presents psychological problems about reproduction. Because of infertility and the necessity for assisted reproductive choices, many people with TS feel psychological and socially stressed. For these patients, psychological assistance and genetic counseling are crucial elements of fertility treatment because they enable them to manage the emotional and social consequences of infertility and grasp the genetic elements of TS. For women with Turner syndrome, this kind of help together with a multidisciplinary approach to reproductive therapy may greatly enhance quality of life and results of treatment (Oktay *et al.*, 2016; Yetman *et al.*, 2021) ^[56, 55].

Gene mutations and their effect on IVF outcomes

By influencing ovarian response, embryo quality, and implantation success, gene abnormalities impacting reproductive processes may dramatically alter *in vitro* Fertilization (IVF) results. Linked to Fragile X-Associated Primary Ovarian Insufficiency (FXPOI), mutations in the FMR1 gene have been shown to compromise ovarian function (Agustí *et al.*, 2024) ^[57]. Women with FXPOI frequently have low ovarian reserve, which results in less oocytes obtained during IVF cycles and hence lowers their chances of successful pregnancy. Lower embryo quality linked with FMR1 mutations has further complicated IVF success rates and raised the risk of cycle cancellation or embryo transfer failure (Sherman *et al.*, 2016) ^[58].

IVF results also depend critically on mutations in genes controlling hormonal pathways including those of the LH and FSH receptor genes (LHR and FSHR). For example, some FSH receptor gene (FSHR) mutations might cause resistance to follicle-stimulating hormone, therefore restricting the ovarian response to IVF. Higher dosages of

hormonal stimulation are usually required for this resistance, which increases cycle expenses and, sometimes reduces oocyte yields. Particularly in patients with inexplicable low ovarian response during IVF cycles, such alterations highlight the need of genetic screening in forecasting ovarian response (Rivero-Müller & Huhtaniemi, 2022) ^[59].

Given the important function of mitochondria in oocyte quality and embryo development, mitochondrial DNA (mtDNA) abnormalities also affect IVF results. Lower oocyte viability and more embryonic fragmentation follow from reduced energy generation caused by mutations in mitochondrial genes. Research indicates that high mtDNA mutation embryos have lower implantation rates and more risk of developmental halt. Considering these consequences, mtDNA screening in IVF has been investigated as a possible instrument to evaluate embryo viability especially for individuals with a history of recurrent implantation failure (Zhang & Wu, 2023) ^[60].

Known for their part in folate metabolism, mutations in the Methylene tetrahydrofolate Reductase (MTHFR) gene may also affect IVF effectiveness. Particularly specific mutations like MTHFR C677T have been linked to altered methylation patterns influencing embryo development and implantation. Higher homocysteine levels have been associated to this mutation, which may adversely affect placental development and raise the chance of early pregnancy loss. MTHFR gene screening is therefore often advised for women experiencing recurrent pregnancy loss or poor IVF results to better guide therapy and supplementing plans (Enciso *et al.*, 2016) ^[61].

Maternal tolerance of the embryo may be influenced by gene alterations influencing immunological function, like those in the HLA-G gene. Because of their effect on the mother immunological response, especially the control of Natural Killer (NK) cell activity, HLA-G mutations have been linked with lowered embryo implantation rates. Because their immune systems may not sufficiently support the early stages of pregnancy, women with certain HLA-G gene variants may have higher rates of implantation failure or miscarriage. Thus, it has been advised that a technique to maximize embryo selection and enhance IVF results is genetic screening for HLA-G mutations (Hunt *et al.*, 2005; Lyngé Nilsson *et al.*, 2014) ^[62, 63].

Conclusion

IVF results are highly influenced by genetic elements including particular gene mutations, chromosomal abnormalities, and polymorphisms. This study emphasizes how changes in genes linked to ovarian function, hormone control, and embryo development may greatly influence IVF procedures and shows the complicated interaction between genetic predispositions and reproductive success. Reduced fertility, poor embryo quality, and higher risk of implantation failure or miscarriage have been linked to genetic variations in hormone receptor genes (e.g., FSHR, LHR), chromosomal abnormalities including aneuploidy and mosaicism, and gene mutations in mtDNA, MTHFR, and FMR1.

By helping to choose viable embryos and customizing procedures catered to individual genetic profiles, the incorporation of genetic screening including Preimplantation Genetic Testing (PGT) for aneuploidies and structural rearrangements holds promise for enhancing clinical results in IVF. Furthermore, knowing the genetic

causes of diseases linked to infertility include Turner syndrome, PCOS, and early ovarian insufficiency helps doctors create individualized treatment programs, therefore improving the odds of successful conception and pregnancy. Future studies should concentrate on clarifying the genetic causes of infertility and investigating IVF use of cutting-edge genetic technology. This information may help to enable more customized, efficient methods of reproductive therapy, therefore improving the results for individuals with complicated genetic backgrounds. IVF success rates may rise with ongoing improvements in genetic screening and tailored reproductive therapy, therefore offering fresh hope to people dealing with infertility.

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