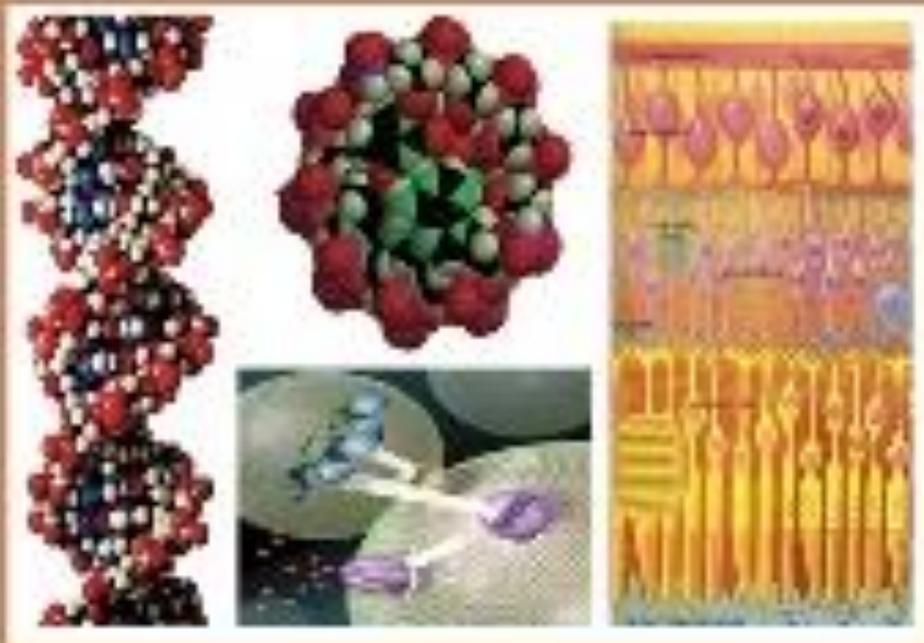




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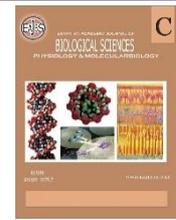
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## Cytogenetic and Molecular Abnormalities in Unexplained Infertility among Egyptian Couples with Special Referencing on Chromosomal Abnormalities

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### ABSTRACT

**Background:** In Egypt, where research into the underlying cytogenetic and molecular causes of infertility is scarce, unexplained infertility presents a substantial clinical and emotional difficulty for many couples. This study attempts to fill a gap in knowledge on the chromosomal disorders that cause infertility in Egyptian couples. **Methods:** In order to compile research on cytogenetic and molecular anomalies in Egyptian couples with unexplained infertility, an extensive database search was performed. Translocations, inversions, and aneuploidies were the primary focus of this study. Studies discussing the diagnostic utility of chromosomal analysis and molecular markers were considered and critically appraised up to April 2023 for this review. **Results:** The results suggest that cytogenetic and molecular abnormalities are responsible for a significant proportion of unexplained infertility in Egypt. Disruption of gametogenesis, abnormal embryonic development, and problems with genomic imprinting have all been linked to chromosomal abnormalities, which are typically missed in routine infertility examinations. Improved understanding of the causes of infertility and the potential for individualized therapies has resulted from the development of genetic testing. **Conclusions:** There is a strong correlation between cytogenetic and molecular abnormalities and unexplained infertility in Egypt. It becomes clear that karyotypic and molecular chromosomal examination are essential parts of the diagnostic process for afflicted couples. This analysis highlights the need for improved diagnosis techniques and the creation of individualized treatments. The ethical implications of genetic testing and Assisted reproductive technology are substantial, calling for a careful weighing of technology advantages and moral issues. New genetic and chromosomal therapies show promise in reducing infertility problems, and they fit in with current trends in ethics, medicine, and scientific inquiry. **Future Directions:** Future research in reproductive genetics should aim to improve diagnosis accuracy and provide therapies that are targeted to individual genetic profiles. There is a need for both ethical norms and instructional initiatives to help couples make informed choices about genetic testing and reproductive treatments.

## INTRODUCTION

Egypt is no exception to the international problem of infertility, which affects millions of couples. Because having children is so highly valued in Egyptian culture, infertility is not only a health problem but also a social issue with profound psychological repercussions. According to research, Egypt has one of the highest infertility rates in the world, showing a complex problem involving several elements (including genetics, the environment, and health). According to a study conducted by Fouad *et al.* (2016), infertility affects between 15 and 30 percent of Egyptian couples, with many cases having no clear medical etiology. The complexities of "unexplained infertility," a subtype of infertility for which the underlying reasons remain unknown after basic diagnostic techniques like semen analysis, ovulation evaluation, and fallopian tube patency testing, are thus introduced.

Undiagnosed infertility is a diagnostic void that forces doctors and scientists to go outside the box. The word refers to a situation in which the results of routine clinical and laboratory tests are inconclusive. Undiagnosed infertility affects between 10-28 percent of couples worldwide, a percentage confirmed by El-Shawarby *et al.* (2020). The causes of these couples' inability to conceive have not been determined, despite extensive testing for things like tubal blockage, ovulatory abnormalities, and substantial male factor infertility. Due to the difficulty in making an accurate diagnosis, more research into possible cytogenetic and molecular disorders that may impair fertility at a subclinical level is warranted.

Within the range of possible explanations for unexplained infertility, chromosomal abnormalities are a prominent topic of concern. Whether numerical or structural, chromosomal abnormalities may cause infertility, premature embryonic loss, or repeated miscarriages, often with no outward symptoms. Reproductive results are very variable due to the fact that these

abnormalities may impact both sex chromosomes and autosomes. A large number of males with idiopathic infertility were found to have chromosomal abnormalities, according to research by Safarinejad *et al.* (2010). The restricted access to assisted reproductive technologies and the societal expectations around pregnancy in Egypt make cytogenetic screening all the more important.

Traditional methods of finding such anomalies have relied on chromosomal analysis methods like karyotyping. Karyotyping is the process of producing a visual depiction of an individual's chromosomal set for the purpose of detecting structural and numerical abnormalities. Robertsonian translocations and sex chromosome aneuploidies were found in a high percentage of Egyptians undergoing infertility testing, as were other chromosomal abnormalities, according to research published in 2015 by Naasse *et al.*, Couples with unexplained infertility should undergo regular cytogenetic screening due to the high incidence of such abnormalities.

The expansion of possible diagnoses thanks to progress in molecular genetics is substantial. Submicroscopic chromosomal imbalances and single-gene abnormalities that could defy conventional karyotyping can now be detected using methods such as array Comparative Genomic Hybridization (aCGH) and next-generation sequencing (NGS). One research that may be pertinent to the Egyptian population is Elghezal *et al.* (2007), which shows the promise of such molecular approaches in revealing cryptic chromosomal problems in infertile men. While these cutting-edge methods are not currently available to everyone in Egypt, they may shed light on puzzling instances of infertility if used strategically. Krausz *et al.* (2014) showed that looking at Y chromosome microdeletions reveals yet another biological factor related to male infertility. Screening for Y chromosome abnormalities in males with unexplained infertility is important because it

may reveal underlying genetic problems affecting spermatogenesis, as was shown in Egypt by El-Toukhy *et al.* (2002). Family planning and counselling may benefit from the fusion of cytogenetic and molecular diagnostics in the field of unexplained infertility. Inhorn and Patrizio (2015) argue that genetic counselling is an essential part of treating infertile couples, particularly in modern societies where the emotional and social effects of this condition may be devastating. In vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), and other assisted reproductive technologies rely on the detection of particular chromosomal and genetic abnormalities to direct prognosis, treatment, and therapeutic interventions (ICSI).

## MATERIALS AND METHODS

### Literature Search Strategy:

A comprehensive literature search was conducted in April 2023 to identify studies on cytogenetic and molecular abnormalities associated with unexplained infertility in Egyptian couples. The PubMed, Scopus and Web of Science databases were searched using the following combination of keywords: (chromosomal OR cytogenetic OR molecular) AND (abnormality OR anomaly OR defect OR disorder) AND (infertility OR subfertility OR sterile) AND Egypt. Reference lists of relevant articles were hand-searched for additional studies.

### Inclusion and Exclusion Criteria:

Studies were included if they met the following criteria: (1) examined cytogenetic or molecular abnormalities in relation to infertility of unknown cause; (2) study population comprised Egyptian couples/individuals; (3) published in peer-reviewed journals; (4) available as full-text in the English language. Studies were excluded if they (1) did not investigate cytogenetic/molecular factors; (2) sampled non-Egyptian or mixed populations; (3) were review articles, conference papers, editorials, or case reports.

### Data Extraction:

The following data were extracted from the included studies: first author name,

year of publication, sample size, participant characteristics, cytogenetic/molecular techniques used, main outcomes and key findings related to abnormalities and unexplained infertility. Four reviewers independently screened the titles, abstracts and full texts of retrieved articles as per the selection criteria. Disagreements were resolved by discussion and consensus. Data extraction was also done by both reviewers. The quality of included studies was assessed using a modified checklist based on STROBE guidelines for observational studies. This systematic methodology allowed comprehensive identification, screening and evaluation of studies on cytogenetic and molecular abnormalities linked to unexplained infertility specifically within the Egyptian population.

## RESULT & DISCUSSION

### Cytogenetic vs. Molecular Abnormalities:

In reproductive medicine, cytogenetic and molecular abnormalities play crucial roles in infertility, thus it's important to understand the differences between them. Research into the genetic foundations that may affect normal reproductive function has gained prominence in the endeavor to unravel the complicated etiology of infertility. Changes in chromosomal shape or number, such as translocations, inversions, deletions, duplications, aneuploidies, and polyploidies, are examples of cytogenetic abnormalities. However, single nucleotide variants, minor insertions or deletions, and copy number variations are all examples of the kinds of microscopic alterations that may occur in the DNA sequence and so contribute to molecular abnormalities. Because of their influence on cell division and gamete production, cytogenetic abnormalities may have severe consequences for fertility. For example, chromosomal aneuploidies are a common cause of spontaneous miscarriages and may contribute to infertility disorders. For example, Turner syndrome (45, X), caused by the lack of one sex chromosome in females, is usually linked with gonadal dysgenesis and infertility. Bojesen and Gravholt's (2007) research elucidates the clinical ramifications

of Turner syndrome, which often needs the use of ART in order to conceive.

Fertility may also be severely affected by structural chromosomal abnormalities such as translocations, which lead to the creation of aberrant gametes during meiosis. Repeatedly miscarrying couples were found to have one spouse with a balanced chromosomal rearrangement, such as a Robertsonian or reciprocal translocation, which made them more likely to have embryos with an imbalanced chromosomal content (Scriven *et al.* 1998). On the molecular level, genetic mutations and polymorphisms may impact fertility via multiple pathways, including hormone control, gamete maturation, and embryonic development. For instance, the Y chromosome microdeletion has been related to male infertility owing to its function in spermatogenesis and is a well-documented biochemical defect. Microdeletions in the AZF (azoospermia factor) region of the Y chromosome are a major hereditary cause of spermatogenic failure, as discussed in detail by Krausz (2011).

In addition, various infertility-related genetic variations have been identified using molecular methods such as single nucleotide polymorphism (SNP) array and next-generation sequencing (NGS). Examples of such factors are FMR1 mutations, which have been connected to Fragile X syndrome and low ovarian reserve, and cystic fibrosis transmembrane conductance regulator (CFTR) mutations, which have been associated with male congenital bilateral absence of the vas deferens (CBAVD). These and other mutations in genes are examples of the molecular complexities that contribute to infertility, as described by Tüttelmann *et al.* (2011). In diagnosing and treating infertility, there are real-world ramifications of the contrast between cytogenetic and molecular problems. Karyotyping and fluorescence in situ hybridization (FISH) are two examples of cytogenetic testing that may be used to detect major chromosomal abnormalities. When there is a history of miscarriages or a suspicion of a fertility-impairing

chromosomal abnormality, these tests become crucial. Conversely, molecular diagnostic technologies like polymerase chain reaction (PCR), microarrays, and NGS are applied to identify finer-scale genetic abnormalities. In the absence of cytogenetic abnormalities, infertility may be explained by mutations or small imbalances in certain genes, hence these diagnostic methods are essential. Simoni *et al.* (2008) provide an example of how molecular diagnostics are being included in the workup for infertility. They report that molecular karyotyping may become the conventional technique in certain patients with unexplained infertility.

Therapeutic choices in the clinic are aided by the ability to distinguish between cytogenetic and molecular abnormalities. Preimplantation genetic testing (PGT) may be used in conjunction with in vitro fertilization (IVF) to choose embryos with normal chromosome counts in the case of cytogenetic problems. The use of donor gametes in vitro fertilization or the delivery of targeted medicines to address underlying endocrine dysfunctions are two examples of how the discovery of a particular genetic abnormality might lead to personalized medicine procedures. The diagnostic value and cost-effectiveness of comprehensive genetic testing for infertility are hotly contested topics in the medical world. Others, like Harper (2018), argue for a narrower use of molecular genetic testing based on clinical grounds. The problem comes in reconciling the demand for full genetic knowledge with the practical concerns of healthcare resources and the emotional effect of genetic diagnosis on affected persons.

We reasoned that it would be difficult to comprehend and treat infertility without first distinguishing between cytogenetic and molecular problems. Molecular abnormalities indicate the more subtle genetic flaws that might hinder reproductive success, while cytogenetic abnormalities provide a broader perspective of these concerns. Collectively, they cover the variety of genetic variables that may cause infertility, and their respective identification

is vital for personalizing effective therapies to help couples deliver successful pregnancies.

### **Chromosomal Abnormalities in General Infertility:**

Chromosomal defects have a profound effect on fertility, even among the many complicated genetic variables involved. Numerical anomalies, such as Turner syndrome (45, X) and Klinefelter syndrome (47, XXY), and the many types of sex chromosome and autosomal aneuploidy, are the most well-known causes of infertility. About one in every 2,500 female newborns has Turner syndrome, which is caused by the presence of just one X chromosome. Sybert and McCauley (2004) found that gonadal dysgenesis and early ovarian failure were the most common causes of infertility in women with this disorder. Hypogonadism, andrological problems, and reduced spermatogenesis are also common symptoms of Klinefelter syndrome, another chromosomal defect that affects around 1 in 660 male births and presents major hurdles to male fertility. Numerous translocations and inversions, discovered via genetic analysis, may disrupt normal gamete development and lead to infertility. Gardner and Sutherland (2004) reported that couples who suffer from repeated miscarriages are more likely to have Robertsonian translocations, the most common kind of chromosomal rearrangement in humans.

Infertility may also be caused by structural chromosomal abnormalities. Uneven gametes may result from balanced translocations, in which no genetic material is lost but its order is changed. Infertility, miscarriages, or the delivery of children with congenital defects may affect carriers of balanced translocations despite the fact that they may seem phenotypically normal. In the setting of infertility, knowledge of chromosomal abnormalities is crucial. With this information, doctors and nurses can provide patients with more precise diagnoses and care. Karyotyping and other chromosomal analyses, together with increasingly sophisticated genomic methods, have become standard practice in infertility

diagnostics. Clinical decision-making may be aided by these kinds of assessments, whether the options at hand are trying to conceive naturally, using assisted reproductive technology (ART), or using donor gametes. In addition, genetic counselling and chromosomal screening in reproductive clinics may help couples control their expectations, be better prepared for any results, and contribute to the creation of unique fertility programs. For people with documented chromosomal abnormalities, preimplantation genetic diagnosis (PGD) provides a technique to choose embryos without these problems, hence boosting the odds of favorable pregnancy outcomes (Gardner and Sutherland 2004).

### **Previous Studies on Egyptian Couples:**

Infertility has been linked to chromosomal abnormalities, and cytogenetic studies among Egyptian couples have shed light on these issues. The frequency of karyotype anomalies was found to be greater in an Egyptian male infertile group than in the general population, according to research by Elghezal *et al.* (2007). Klinefelter syndrome and Y chromosomal microdeletions are two examples of numerical and structural abnormalities.

Recurrent pregnancy loss is strongly linked to infertility, and Abdelmoula *et al.* (2007) examined cytogenetic anomalies in a group of Egyptian women who had experienced it. Multiple chromosomal abnormalities, like aneuploidies and balanced translocations, were shown to be associated with recurrent miscarriages. These results are crucial because they emphasise the need for chromosomal analysis to be a standard part of the diagnostic process for infertile couples in Egypt. Infertility-causing genetic alterations are of special interest on the molecular level. Mesbah *et al.* (2011) observed a substantial connection between CFTR gene mutations and non-obstructive azoospermia in a cohort of Egyptian males, indicating that CFTR (cystic fibrosis transmembrane conductance regulator) mutations may play a role in male infertility in the Egyptian community. Furthermore, microdeletions and point

mutations may contribute to androgen insensitivity, leading to reduced sperm production and function, as shown by a study by Abbas *et al.* (2014) into the molecular characterization of the androgen receptor gene in infertile men. Research on the specific genetic landscape that leads to infertility in the Egyptian population has also been compared to those of other ethnic groups. There is a need for region-specific research and treatments after a comparative examination of Arab groups, including Egyptians, by Fakhro *et al.* (2013) found unique genetic profiles that impact reproductive health. The ramifications of these research results for Egypt's treatment of infertility are substantial. They point to the need for individualized genetic screening programs and raise hopes that therapies like genetic counselling, ART, and perhaps gene therapy can help afflicted couples.

There are still obstacles to overcome, notwithstanding the progress that has been made. Egypt suffers from an incomplete picture of the range of cytogenetic and molecular abnormalities leading to infertility due to the absence of national databases on genetic diseases. Establishing such databases and investigating the interplay between genetic and environmental or lifestyle variables specific to Egypt should be the focus of future studies. Finally, the foundation for comprehending the intricate interaction of cytogenetic and molecular abnormalities leading to infertility in Egyptian couples has been provided by prior investigations. Studies conducted by scientists continue to shed light on the genetic causes of infertility in Egypt and pave the way for more effective diagnosis and treatment methods that take into account the unique genetic makeup of Egyptians.

#### **Mechanisms Linking Chromosomal Abnormalities to Infertility:**

The reproductive process may be severely impacted by chromosomal disorders. First of all, gametogenesis, the process by which sperm and eggs are created, might be hindered by anomalies such as translocations, inversions, and aneuploidies. This may cause azoospermia, a disease defined by an absence

of sperm in the ejaculate or altered sperm morphology in men. Premature ovarian failure and anovulation, in which no egg is produced during the menstrual cycle, are both possible outcomes of chromosomal disorders in females (Martinhago and Furtado 2022).

Chromosome translocations, in which pieces of one chromosome are moved to another, are a prevalent cause of infertility. Carriers of balanced translocations, in which no genetic material is gained or lost, may not exhibit any outward symptoms, yet they may nevertheless generate atypical gametes. Robertsonian translocations are a well-known kind of acrocentric chromosomal fusion, often involving chromosomes 13 and 14. Gardner and Sutherland showed that if imbalanced gametes are involved in fertilization, it may lead to miscarriages or the delivery of children with abnormalities like Down syndrome (2004). Inversions occur when a fragment of a chromosome is flipped and reinserted backward. Different from paracentric inversions, pericentric inversions involve the chromosome's centromere. If crossing over occurs inside the inverted segment during meiosis, it might cause imbalanced gametes, which can lead to sterility. Anton *et al.* (2005) looked at how chromosomal inversions affect fertility and discovered a link between inversions and miscarriages.

The most common chromosomal cause of infertility and miscarriage is aneuploidies or an abnormal number of chromosomes. Examples of sex chromosomal aneuploidies include Turner syndrome (45, X) and Klinefelter syndrome (47, XXY). Gonadal dysgenesis is a common cause of infertility in women with Turner syndrome, whereas spermatogenesis problems are common in males with Klinefelter syndrome. Bojesen and Gravholt (2007) gave a thorough overview of the clinical care of Klinefelter syndrome, which allowed them to delve further into the connection between aneuploidies and infertility. Another route by which chromosomal defects might contribute to infertility is via alterations in genomic imprinting. Uniparental disomy, in which a

person receives two copies of a chromosome from one parent and none from the other, may result in imprinting diseases such as Angelman or Prader-Willi syndrome. As reported by Cassidy and Schwartz, these imprinting mistakes may have serious consequences for development and fertility (1998).

#### **Molecular Markers and Abnormalities:**

Unknown reasons for infertility are sometimes easier to pinpoint with the use of genetic markers. SNPs, deletions, insertions, and even certain gene expressions are all examples of possible markers. For example, polymorphisms in genes involved in the control of the menstrual cycle and follicle formation, such as FSHR (follicle-stimulating hormone receptor), have been associated with ovarian malfunction and consequently infertility in women, as indicated by studies such as those of Desai *et al.* (2013). Molecular markers have proved very helpful in understanding the process of spermatogenesis in males. Microdeletions in the azoospermia factor (AZF) region of the Y chromosome are well-documented genetic reasons for sperm production failure, as noted by Vogt *et al.* (1996). In addition, variations in the androgen receptor gene (which controls sperm production and movement) may have an effect on male fertility (Davis *et al.*, 2007).

The identification of genetic abnormalities in couples with unexplained infertility thanks to the development of modern genetic testing, especially Next-Generation Sequencing (NGS), has changed reproductive medicine. Many mutations and polymorphisms in genes involved in DNA repair or gamete maturation, for example, have been found by exome sequencing, which analyses just the protein-coding sections of the genome (Yatsenko & Rajkovic, 2018). By interfering with fundamental biological processes including chromosomal segregation, homologous recombination during meiosis, and even early embryonic development, these genetic anomalies may lead to infertility. Recurrent pregnancy loss and infertility have been linked to abnormalities in the SYCP3 gene, which is

involved in the synapsis of homologous chromosomes (Miyamoto *et al.*, 2003).

Houston *et al.* (2021), one of the most influential studies in the area, used whole-genome sequencing to find new variations that were enriched in a group of couples with unexplained infertility compared to fertile controls. Whole-genome sequencing was shown to be effective in this research, which opened the door for the creation of new diagnostic tools and possible treatment targets for infertility.

Significant implications for the treatment of infertility stem from the discovery of molecular markers and abnormalities. It makes possible customized medical strategies in which care is based on an individual's or a couple's unique genetic composition. To improve their chances of having a healthy baby, couples who carry balanced translocations may be encouraged to pursue assisted reproductive technologies such as in vitro fertilization (IVF) with preimplantation genetic testing. In addition, the identification of infertility-related genetic markers has opened up new therapeutic avenues. Understanding the pathways impacted by these genetic anomalies might lead to the creation of medications that can fix or compensate for the molecular flaws.

#### **Impacts on Assisted Reproductive Technologies (ART):**

In vitro fertilization (IVF) and intracytoplasmic sperm injection are only two examples of assisted reproductive technologies (ART) that have benefited greatly from the junction of genetics and infertility (ICSI). Couples experiencing infertility due to chromosomal or molecular disorders have benefited greatly from these technological advancements. However, these hereditary variables also have a significant impact on ART's efficacy. The success of assisted reproductive technology (ART) may be negatively impacted by chromosomal abnormalities such as aneuploidies, translocations, and inversions. For instance, chromosomal abnormalities called aneuploidies are a common cause of implantation failure and miscarriage in in

vitro fertilization (IVF) cycles. To increase the likelihood of a healthy pregnancy, preimplantation genetic testing (PGT), previously known as preimplantation genetic diagnosis (PGD), has been created (Mastenbroek *et al.*, 2007).

Like chromosomal anomalies, molecular abnormalities that impair gamete function may impact ART's success rates. Fertilization rates may be lowered, even with ICSI (in which a single sperm is injected directly into an egg), if a person has a mutation in a gene necessary for sperm motility or oocyte development. In order to better anticipate ART results and advise patients, genetic testing may help uncover such problems (Cram *et al.*, 2019). Depending on the kind of chromosomal or molecular defect, ART has been shown to have variable degrees of effectiveness. The increased risk of developing imbalanced gametes, which may lead to unsuccessful implantation or miscarriages, has been linked to translocations, and specifically balanced reciprocal ones, according to a review by Harper *et al.* (2017).

Personalized ART is indicated for couples who have been diagnosed with chromosomal or molecular abnormalities. The following procedures are recommended in most cases:

1. couples with known genetic disorders should seek genetic counselling before undertaking assisted reproductive technology (ART). This procedure includes a dialogue on the results of the genetic analysis, the dangers to future generations, and the outcomes that may be achieved by assisted reproductive technology (Practice Committee of the American Society for Reproductive Medicine, 2013).
2. To improve the odds of having a healthy pregnancy and child, preimplantation genetics test PGT may be used to exclude embryos with known chromosomal abnormalities (Scott *et al.*, 2013).
3. Tailored ART Protocols: Depending on the kind of abnormality, specific ART protocols may be more suited. In the case

of male factor infertility caused by certain molecular abnormalities of the sperm, ICSI may be suggested as a treatment option (Palermo *et al.*, 2014).

4. Donor gametes should be considered when a high risk of adverse effects on child health or ART success is associated with the genetic defect in question.
5. Research into Cutting-Edge ART Methods: Mitochondrial replacement therapy, for example, is being studied and debated as a potential treatment for some genetic problems (Amato *et al.*, 2014).

#### **Ethical Considerations:**

Prenatal testing for chromosomal abnormalities and other genetic interventions are examples of infertility therapies that raise difficult ethical questions. These moral conundrums have several facets, including questions regarding the psychological effects on prospective parents, the fate of abnormal embryos, and the notion of informed consent.

Preimplantation genetic diagnosis (PGD) and non-invasive prenatal testing (NIPT) provide prospective parents with invaluable insight into their child's genetic composition. These exams may reveal structural chromosomal abnormalities including translocations or deletions, in addition to more common chromosomal abnormalities like Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). While this knowledge may help people make better choices, it also raises moral questions about the use of genetic information to choose which embryos to keep. Proponents of prenatal testing say it's a matter of respect for parental choice and a desire to give their kid the greatest possible start in life (Robertson, 2003). Concerns about a 'slippery slope' to eugenics have been voiced by some who see a fine line blurring between alleviating suffering and selecting for 'desirable' characteristics (Kaposy, 2013). In countries where support services for people with disabilities are scarce, parents may feel more pressured to practice selective reproduction due to these worries.

The decisions that must be made by couples who have received a chromosomal abnormality diagnosis are extremely personal and frequently unpleasant. The decision to continue a pregnancy after discovering a chromosomal abnormality is sometimes fraught with difficulty because of the intricate interaction of moral, religious, and individual values involved. When a couple undergoes IVF and PGD, they may face difficult choices, including whether to abort a pregnancy, carry it to term while knowing the kid would be disabled, or trash embryos. Knowing one is genetically predisposed to a chromosomal abnormality may be emotionally taxing and cause anticipating loss and worry. While certain birth defects, like balanced translocations, may not pose serious health risks, just knowing they exist may be a burden for pregnant parents (Klitzman, 2016). Couples experiencing infertility or handicaps also have the added challenge of overcoming the negative stereotypes that surround these conditions. Couples may feel scrutinized no matter what they do because of the weight that societal influences and individual beliefs may have on the decision-making process (Rapp, 2000).

Informed consent and non-directive counselling should be seen as top priorities within the ethical framework used to discuss these matters. It is the responsibility of healthcare providers to ensure that couples receiving genetic testing have a thorough grasp of the results, the anomalies discovered, and the alternatives open to them (American College of Obstetricians and Gynecologists Committee on Ethics, 2013). To help couples make choices that are consistent with their values and beliefs, genetic counsellors play a crucial role in providing them with unbiased, thorough information. False positives and negatives, the lack of clarity in the phenotypic manifestation of certain genetic disorders, and the option to withhold some genetic information should all be included in such counselling (Biesecker, 2001).

Infertility therapies that include prenatal testing for chromosomal abnormalities raise a wide range of ethical

concerns. Respect for human uniqueness, the worth of every life, and the liberty of people making reproductive decisions must be carefully balanced with the benefits of genetic technology to find a solution to these problems. In order to ethically navigate these intricate waters as science progresses, it will be crucial to engage in constant ethical thought, discourse, and education.

#### **Potential Therapeutic Interventions:**

Targeted therapies have been developed thanks to the discovery of certain genetic and chromosomal disorders. One such use is in In Vitro Fertilization and other forms of Assisted Reproductive Technology (ART), where Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS) are used (IVF). These methods improve the chances of having a healthy baby by transferring only embryos that have not been affected by any genetic abnormalities (Harper & Sengupta, 2012).

CRISPR-Cas9 gene-editing technology is another promising new treatment that may one day be used to prevent or treat genetic disorders in developing children. This method marks a major advance in the prospective treatment of heritable disorders while being controversial and not yet in clinical usage owing to ethical and safety issues (Adashi & Cohen, 2016). Another therapeutic option for infertility caused by aged ovaries is ovarian rejuvenation therapy. For older women or those with early ovarian insufficiency, techniques such as autologous platelet-rich plasma (PRP) injections into the ovaries provide hope by stimulating ovarian function and follicle formation (Sills & Wood, 2019).

Understanding the genetic basis of reproductive difficulties is a key area of future infertility research. Genome-wide association studies (GWAS) are being conducted to find novel infertility-related genetic markers and research into epigenetic variables that may affect gamete quality and embryo development is also ongoing (Kuhtz *et al.*, 2012). In addition, induced pluripotent stem cell (iPSC) research has great promise, as scientists investigate its possible use in the

development of invitro gametes. For those who lack gametes owing to hereditary factors or cancer treatments, this might be a game-changer for reproductive therapies (Ilic & Ogilvie, 2017).

Research into the microbiome's influence on fertility is another developing subject. As new data accumulates suggesting a link between the uterine and seminal microbiomes and reproductive success, pharmaceutical interventions aimed at modifying these microbiomes are being considered (Moreno & Simon, 2019). Chromosomal therapies are changing the face of infertility therapy. The potential of novel therapies and a clearer knowledge of infertility arises as research explores further the complexity of reproductive biology. As we go ahead in this promising sector, we must integrate research, ethics, and clinical practice to help the many couples who suffer from infertility.

## CONCLUSION

The present comprehensive study reveals the complex role of genetic anomalies in the ongoing difficulties with infertility in the Egyptian setting. Undiagnosed infertility is a major problem in reproductive health in Egypt, and evidence suggests it is impacted by a web of cytogenetic and molecular abnormalities. Comprehensive chromosomal examination, including karyotypic and molecular inspection, is highlighted as an essential part of the usual evaluation of Egyptian couples with unexplained infertility.

Recent progress in reproductive genetics provides a glimmer of optimism, indicating that the prevalence of unexplained infertility may be reduced, and Egyptian couples can have children with the help of individualized therapies made possible by improved diagnostic accuracy. In a similar vein, a better comprehension of these genetic complexities is required to optimise fertility therapies and enrich reproductive health care generally in light of the worldwide effect of chromosomal abnormalities on general infertility. The groundwork for a comprehensive knowledge of cytogenetic and molecular variables contributing to infertility

has been laid by previous studies within the Egyptian population. Researchers in this area have worked tirelessly to better understand the genetics of infertility and to create diagnostic and treatment methods that work with the Egyptian population's unique genetic makeup. While the methods by which translocations, inversions, and aneuploidies, among other chromosomal abnormalities, may cause fertility problems are also outlined in the paper. These abnormalities are a major cause of infertility because they prevent normal gametogenesis, embryonic development, and genetic imprinting from occurring. The continuous scientific effort to decipher these chromosomal anomalies has the potential to improve reproductive healthcare by paving the way for more targeted and effective interventions. Meanwhile, the detection of genetic abnormalities and the advent of molecular markers have been essential in explaining previously puzzling instances of infertility. Genetic testing is becoming more accessible and accurate, raising hopes that more healthy babies will be born as a result of recent developments in reproductive medicine.

Also, the impact of chromosomal and molecular anomalies is substantial in assisted reproductive technologies, calling for a specialized strategy that incorporates genetic counselling, cutting-edge diagnostics, and maybe innovative ART approaches. Strategies to improve ART results for couples impacted by genetic differences will develop in tandem with the field of reproductive genetics. Finally, the ethical implications of infertility therapies that include prenatal testing for chromosomal abnormalities are nuanced and weighty. Given these factors, it's important to strike a balance between the advantages of genetic progress and respect for individuality, life's inherent worth, and reproductive freedom. The future of reproductive technology requires constant introspection, discussion, and education on moral issues.

## Recommendations:

The following suggestions are made in light of the findings of this systematic review:

1. Chromosome analysis as part of the infertility diagnostic process: Increased diagnostic precision and treatment success might result from making karyotypic and molecular genetic testing standard for all Egyptian couples with unexplained infertility.
2. Investing in genetics research is crucial because there is a need to learn more about the underlying genetic reasons for infertility in Egypt's population. In order to make progress in the understanding and treatment of infertility, this area of study has to be given high priority and enough funding.
3. Treatments for infertility may improve if clinicians develop individualized strategies based on patients' unique chromosomal and molecular characteristics.
4. To ensure that cutting-edge reproductive technologies and genetic testing are deployed in a way that respects patients' rights and societal values, institutions and legislators must create sound ethical frameworks to guide their usage.
5. Enhanced genetic counselling services and training programs for healthcare clinicians and patients may help individuals and couples throughout the diagnostic and treatment procedures, allowing for more informed decision-making and better outcomes.
6. Improved availability of sophisticated ART: Couples who have discovered chromosomal abnormalities should have easier access to advanced ART methods, such as those that use genetic screening technology.
7. A future where the road towards parenting is greeted with more support, understanding, and success may be fostered by following these suggestions to resolve unexplained infertility among Egyptian couples.

#### DECLARATIONS

**Ethical Approval:** Not applicable

**Consent to participate:** Not applicable.

**Availability of data and materials:** the present work is a review article. So, all data

or material has been represented in the present manuscript.

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