REVIEW ARTICLE

Current Scenario on Genetic Basis of Infertility- A Review

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ABSTRACT
Infertility is an emerging major health issue affecting the physical, psychological and social status of the general population across the globe. There are innumerable causes of infertility, viz., ovarian and testicular disorders, advanced maternal age, obesity, chromosomal abnormalities etc. Most of these causes are linked to the genetic disorders. With recent advances in the field of reproductive biology, it has become imperative to have a concise knowledge of the genetic basis of infertility, for better outcome in Assisted Reproductive Techniques (ART).

Keywords: Male infertility, Female infertility, Chromosomal abnormalities, Assisted reproductive technology, Genetic mutations

INTRODUCTION

Infertility is one of the major health and social problems faced by a huge population across the globe. Its incidence is in increase in the past few decades, hence needs to be addressed. Infertility is a multifactorial disease of reproductive system associated with severe psychological and social stigma. WHO defines infertility as "the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse". For a woman, infertility (or a state of subfertility) can manifest itself as either:

1. The inability to become pregnant, or
2. An inability to maintain a pregnancy, or
3. An inability to carry a pregnancy to a live birth.

According to a WHO systematic analysis of infertility trends in developing countries worldwide, in 2010, an estimated 48.5 million couples were infertile. 1.9% of child-seeking women aged 20–44 years were unable to have a first live birth (primary infertility) and 10.5% of child-seeking women with a prior live birth were unable to have an additional live birth (secondary infertility).[1] Levels of infertility were similar in 1990 and 2010, showing a decrease in primary infertility by 0.1% and increase in secondary infertility by 0.4%.[1] This indicates that infertility is emerging as a global health issue and it is needed to target its prevention and treatment.

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Many factors are implicated in the aetiology of infertility, be it male associated or attributed to the female partner. These factors may be hormonal, infectious, immunological, surgical or psychological. Most of these factors have genetic basis involving several genes and gene products.

The genetic causes of infertility can be either due to an inherited chromosome abnormality or a single-gene defect inherited from parents to the child. In addition, there is an increased risk of difficulty in conception in case of any family history of premature menopause, endometriosis or other factors.

With the advent of recent developments in the field of reproductive biology and the use of newer techniques likeIntracytoplasmic Sperm Injection (ICSI), pre-implantation genetic diagnosis in conjunction with Assisted Reproductive Technology (ART), a thorough understanding of the genetic causes of infertility has become utmost important to plan the outcome of ART and other infertility treatments.

GENETIC CAUSES OF FEMALE INFERTILITY

Advanced Maternal Age and Aneuploidy

Advanced maternal age has been commonly associated with aneuploidy due to non-disjunction of chromosomes

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during meiosis.Aneuploidy is defined as an increase or decrease in the number of chromosomes in a cell. It is considered as main cause of embryonic loss and poor fertility.[2] Many hypothesis explain the correlation of advanced maternal age with aneuploidy.The "limited oocyte pool" hypothesis suggests that the lower number of antral follicles in older women's ovaries causes the recruitment of suboptimal – premature or postmature – oocytes for ovulation.[3] The number and distribution of chiasmata formed during early prophase I as well as weakened centromeric cohesion, establish a strong predisposition for aneuploidy.[4]

Turner's Syndrome

Turner's syndrome (TS) is characterised by a complete or partial absence of one X chromosome. The most frequent chromosome constitution is 45X.[5] About half the patients have a mosaic chromosome complement, the most common being 45X/46XX (15%), and 6% of patients have 46XXq or 46XXp deletions. In rare cases, a ring X chromosome complement can be identified. Thus, the syndrome might be attributable to a limited amount of genetic material in these chromosomes.[6] The cause of the chromosomal abnormality in patients with a 45X karyotype, whether monozomic or mosaic, is usually nondisjunction during meiosis.[7] Most women with TS (95±98%) are infertile due to gonadal dysgenesis.[8] It is caused by oocyte loss from week 18 of pregnancy onwards or over the first few postnatal months and years.[9] In most 45X patients, the oocyte loss takes place in the early stage of meiotic prophase ± pachytene[10] and results in a streak ovary composed of white fibrous stromal tissue containing no ova or follicular derivatives.[11] However, at puberty a minority, mostly those with mosaic karyotypes, have ovaries with a relatively low number of follicles, so that there is spontaneous pubertal development.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine condition that affects 5%–10% of women. PCOS is marked by hyperandrogenism, hyperinsulinemia, insulin resistance, and chronic anovulation. The genetic basis of PCOS is not known, owing to the difficulties in determining the inheritability of PCOS. PCOS is also characterized by insulin resistance. The elevated insulin levels facilitate secretion of androgens from the ovaries and adrenal glands, leading to hyperandrogenism. Elevated levels of androgens lead to menstrual disturbances and infertility.[12] Widespread changes in transcription and transcriptional regulation in PCOS patients have also been found. First, DNA methylation regulates gene transcription. Forty genes have been shown to be differentially methylated in PCOS patients compared with the corresponding genes in normal individuals.[13] Changes in methylation of EPHX1, LMNA, and GSK3A are associated with PCOS.[14] Although several genes have been associated with PCOS, there is no evidence to suggest that a unique gene or a dominant pathway is the sole causative factor.

GENETIC CAUSES OF MALE INFERTILITY

It is estimated that in about 50% of infertile couples, male associated abnormalities are involved in the aetiology of infertility.[15] Of these, most common cause of male infertility is sperm disorder, ranging from oligozoospermia, azoospermia, abnormal morphology and abnormal motility of spermatozoa. There are certain genetic diseases, most of which are either directly or indirectly associated with sperm abnormalities.

Kleinfelter's Syndrome (47, XXY)

Klinefelter's syndrome is a form of hypergonadotropic hypogonadism and infertility resulting from a supernumerary X chromosome (47, XXY), with an incidence of approximately 1 case in 500 phenotypic males.[16] Classically, Klinefelter's syndrome is characterized by gynaecomastia, small, firm testes with hyalinization of seminiferous tubules, hypergonadotrophic hypogonadism and azoospermia. Its prevalence is 0.1% in the general population[17] and among infertile patients up to 11% of azoospermic and 0.7% of oligozoospermic men reportedly have the 47, XXY karyotype.[18] Some men with Klinefelter's syndrome who have chromosomal mosaicism (46, XY/47, XXY) are fertile. Men with nonmosaic, or complete, Klinefelter's syndrome usually have azoospermia, and only a few have any spermatogenesis.[19, 20]

Deletions in the Y Chromosome

Approximately one-third to one half of the cases of infertility are classified as idiopathic,[21] but they may have an unidentified genetic anomaly. It is estimated that 19% of males diagnosed with idiopathic infertility have Yq microdeletions.[22] It has been estimated that between 50–70% of the non-recombining region of human Y chromosome is composed of a variety of highly repeated DNA elements, the majority of which appear to be unique to the humanYchromosome.[23] Deletions of the Y chromosome are likely to be consequence of these repeated elements causing intrachromosomal recombination. There is a possibility that Y chromosome microdeletions may also contribute to spermatogenic failure.[22]

Myotonic Dystrophy 1

Myotonic dystrophy 1 (DM1) is defined as a hereditary, autosomal dominant multi-system disorder characterized by the development of structural and functional abnormalities in the muscle membrane protein associated with muscular dystrophy, cardiac conduction disorders, cataracts, mental retardation, and endocrine and reproductive defects.[2] Progressive testicular atrophy is a prominent feature and occurs with an incidence of approximately 80%.

Histological abnormalities include hyalinization, atrophy, fibrosis of seminiferous tubules, and reduced sperm numbers.[24] Oligospermia and azoospermia are reported in approximately 73% of DM1 patients.[25]

GENETIC BASIS OF INFERTILITY IN BOTH MALES AND FEMALES

Down's Syndrome

Down syndrome is usually associated with advanced maternal age and is a common example of aneuploidy. Down syndrome is a complex genetic disease resulting from the presence and expression of 3 copies of the genes located on chromosome 21 (trisomy 21). In most cases, the extra chromosome stems from the failure of normal chromosomal segregation during meiosis (meiotic nondisjunction).[26] The nondisjunction event is maternal in <95% of cases, occurring primarily during meiosis I in the maturing oocyte, before conception.[27] Down syndrome occurs with an estimated frequency of 1 in 600 live births and 1 in 150 conceptions.[28]

Women with Downs'ssyndrome are less fertile and may have difficulties with miscarriage, premature birth, and difficult labour. On the basis of evidence that abnormal folate and methyl metabolism can lead to DNA hypo methylation and abnormal chromosomal segregation, few workers hypothesized that the C-to-T substitution at nucleotide 677 (677C → T) mutation of the methylenetetrahydrofolate reductase (MTHFR) gene may be a risk factor for maternal meiotic nondisjunction and Down syndrome in young mothers.[29]

Men with Down syndrome are considered as infertile although the causes of infertility are not known in detail yet. The causes may be hormonal deficits, morphological alterations of the gonads, abnormal spermatogenesis, psychological and social factors related to the mental retardation. Additionally, the extra chromosome 21 has a detrimental direct and indirect effect on the reproductive capacity of the affected male patient.[30]

Cystic Fibrosis

Cystic Fibrosis (CF) is the most common life-shortening genetic disease in Caucasians and is caused by mutations in the gene encoding a cAMP-regulated chloride channel, the CF transmembrane conductance regulator (CFTR).[31] CF is a systemic illness that affects various organ systems including the pulmonary, endocrine, epithelial, gastrointestinal, pancreatic, immune, and reproductive systems.[32] Reduced fertility has also been observed in women with CF.[33] The prominent hypothesis for the decreased fertility in CF females is viscous mucus in the cervix that may create a barrier to sperm passage.[34] The majority of men with cystic fibrosis (CF) have associated congenital bilateral absence of the vas deferens (CBVAD) as a result of which spermatozoa are not transported to the urethra. Hence, no spermatozoa are found in the semen, a condition referred to as obstructive azoospermia.[35] Mutations in the CFTR gene have also been identified in patients with CBAVD, which suggests that this condition is a primarily genital form of cystic fibrosis.[36, 37]

Additionally, CFTR is involved in secretion of endometrial and oviduct HCO3-, which is necessary for sperm capacitation. CFTR is also expressed in the cervix, oviduct, ovary, and uterus, where it regulates fluid control in the female reproductive tract. CF is associated with menstrual irregularities, including amenorrhea, irregular cycles, and anovulation.[38]

Supernumerary Marker Chromosomes

Small supernumerary marker chromosomes (sSMC) are defined as structurally abnormal chromosomes that cannot be identified or characterized unambiguously by conventional banding cytogenetics alone; they are generally equal in size or smaller than a chromosome 20 of the same metaphase spread. Small supernumerary marker chromosomes (sSMC), can lead both to fertility problems and repeated abortions.[39] The rate of sSMC presence in the normal population was recently determined to be 0.044%, but elevated to 0.125% in infertile groups. Distributing the latter group into male and female, there is a gender-specific 7.5:1 difference in sSMCfrequency.[40].sSMC presence is enhanced in the heterogeneous group 'patients with fertility problems' about 3-fold compared to the normal population. It was found out that after sSMC detection in connection with unexplained infertility in ~60% of cases the origin of the sSMC can be characterized by application of the centromere-specific probes for chromosomes 14 and 15.[41] Maternally derived sSMC occurred more frequently than paternally derived sSMC.[41] The mechanisms by which sSMC presence influences fertility are not really understood at present, however, there might be a tendency for amenorrhea or defined abnormalities in the gametes to appear in correlation with acrocentric sSMC and repeated abortions in correlation with non-acrocentric sSMC.

Chromosome Structural Abnormalities

Several kinds of chromosomal abnormalities are associated with infertility: deletion, inversion, mutation, aneuploidy, and translocation. Of these, translocation is most common chromosomal abnormality. A study showed that the frequency of chromosomal translocations was 2.1% in infertile men.[42] Chromosomal translocations can be of many types- Robertsonian translocation, Reciprocal Translocation and these account for 10 % of the causes of male infertility.[43] Robertsonian translocationsare defined as translocations involving acrocentric chromosomes (13, 14, 15, 21, and 22).[44] Carriers of Robertsonian translocations are

phenotypically normal; however, they exhibit reproductive dysfunction, such as oligospermia in males.[45] The incidence of Robertsonian translocations has been estimated to be 0.1% in newborns but the frequency in infertile men in can be as high as 0.7%.[42] Reciprocal translocations, which consist of mutual exchange of chromosomal segments between autosomal and sex chromosomes, are found with a frequency of 0.09% in newborns[46] but 15 times high in infertile men.[42] Chromosomal translocations may cause reductions in testicular volume and testosterone level, which may impact spermatogenesis, resulting in azoospermia or oligozoospermia and thereby, male infertility.[42]

GENE MUTATIONS

Single-gene abnormalities are mutations caused by changes in the DNA sequence of a gene, which produce proteins that allow cells to work properly. Gene mutations alter the functioning of cells due to a lack of a protein. Several gene mutations are involved in infertility, either by causing aberrant pubertal development, by causing deficiency of pituitary hormones or affecting the gonadal functions.

Mutations Affecting Genes Located in Hypothalamus

Mutations of genes expressed in the hypothalamus generally result in hypogonadotrophic hypogonadism, a condition of absent or deficient puberty owing to low serum gonadotrophin,follicle stimulating hormone (FSH), and luteinising hormone (LH). TheKAL1 geneis localised in the pseudoautosomal region of the Xp. Mutations like deletions and point mutations causes Kallmann's syndrome in males. Itis an X linked recessive idiopathic condition, associated with hypo hypogonadotrophic hypogonadism and anosmia.[47] Mutations in AHC gene is implicated in Adrenal hypolplasia which causes delayed puberty and cryptochordism in males.[47] Leptin (LEP) and LEPR genes play an important role in puberty. Leptin (LEP) mutations have been found in a few families of obese subjects, who have irreversible pubertal delay.[48]

Mutations Affecting Genes Located in Pituitary

FSHβ gene have been shown to cause absent or incomplete breast development, low FSH and oestradiol, high LH, and sterility in females[49] and males with FSHβ mutations present with azoospermia, but puberty may be normal or absent in them.[49]

Mutations Affecting Genes Located in Gonads

Mutations affecting gonadal function include gonadotrophin receptors, steroid hormone receptors,steroid synthesis defects,as well as miscellaneous causes. Deletions of portions of the X-chromosome have been reported in a large number of patients, most of which are isolated. In general, deletions affecting Xp11 result in ovarian failure in about half of women, with menstrual function in the other half.[47] SOX9 is a member of a family of transcription factors that contain a Sex determining region of Y chromosome (SRY) - related HMG box (SOX). The SOX9 protein is found in the embryonic potential gonads. Thereafter, it is not seen in developing ovaries but is present in fully developed male gonads. Mutations in SOX9 gene have been found in individuals who are chromosomally male but phenotypically female.[50]

CONCLUSION

The genetic basis of infertility is very complex and is determined by many factors. These factors influence the development of gametes, the reproductive organs- both external and internal, their physiology and the development of embryo and its further differentiation. The genetic disorders can affect females, males or both, causing infertility. Genetic disorders can be chromosomal, single gene mutations or can be multifactorial. Extensive research has been conducted for having a better insight into the genetic basis of infertility.However, in spite of extensive research, there are no well-defined genes that can be used for genetic testing of infertility conditions. Thus, there is a need for newer diagnostic technologies to identify both new and known infertility genes. Newer techniques in the field of ART, like Intracytoplasmic sperm insemination (ICSI), oocyte harvesting & transfer, oocyte & sperm donation, chances of achieving fertility in infertile couples is becoming more promising. With the growing incidence of infertility and growing awareness of general population towards newer approach in the treatment of infertility, especially inassisted reproduction, better understanding in the genetic control of infertility will help the clinicians in planning treatment modality that would prove beneficial to the infertile couples. In the future, pursuing the most promising genetic variants, mutations, or polymorphisms may provide clinically relevant therapeutics for infertile individuals.

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