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REVIEW

Some of the Factors Involved in Male Infertility: A Prospective Review

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Abstract: Infertility is defined as the inability of couples to have a baby after one year of regular unprotected intercourse, affecting 10 to 15% of couples. According to the latest WHO statistics, approximately 50–80 million people worldwide sufer from infertility, and male factors are responsible for approximately 20–30% of all infertility cases. The diagnosis of infertility in men is mainly based on semen analysis. The main parameters of semen include: concentration, appearance and motility of sperm. Causes of infertility in men include a variety of things including hormonal disorders, physical problems, lifestyle problems, psychological issues, sex problems, chromosomal abnormalities and single-gene defects. Despite numerous efforts by researchers to identify the underlying causes of male infertility, about 70% of cases remain unknown. These statistics show a lack of understanding of the mechanisms involved in male infertility. This article focuses on the histology of testicular tissue samples, the male reproductive structure, factors affecting male infertility, strategies available to find genes involved in infertility, existing therapeutic methods for male infertility, and sperm recovery in infertile men.

Keywords: male infertility, spermatogenesis, azoospermia, non-obstructive azoospermia

Introduction

Infertility is defined as the inability of couples to have a baby after one year of regular unprotected intercourse, affecting 10–15 percent of couples.[1–4] According to the latest WHO statistics, about 50–80 million people worldwide suffer from infertility.[5,6] Large-scale studies have shown that about half of all cases of infertility occur due to female factors, 20 to 30 percent male factors, and 20 to 30 percent due to common causes of both gender.[6–8] Recent meta-analysis studies by researchers show that male's factors are present in 20–70 percent of infertility cases.[7,9] These findings are significantly broader than previously reported. However, the wide range of male infertility in meta-analysis studies may not reflect the prevalence of this complication in all parts of the world because of reasons such as the lack of rigorous statistical methods that include bias, heterogeneity in data collection, and cultural constraints. Given the significant contribution of male factors to infertility in couples, as well as high levels of unknown factors in male infertility, a lack of understanding of the underlying mechanisms seems to be one of the most important challenges facing this problem. In this article, we have reviewed the histological studies of testicular tissue specimens, male reproductive structure, factors influencing male infertility, strategies to find genes involved in infertility, available therapeutic methods for male infertility, sperm recovery methods in infertile men, and assisting reproductive method (Figure 1).

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Male's Reproductive Organ

In order to better understand the issues and problems associated with infertility, we first discuss some of the key elements involved in male fertility. Human reproductive organs include the primary and secondary organs. Primary reproductive organs include the gonads (responsible for gamete and hormone production), while the secondary organs include the ducts and glands, which play a role in the growth, maturation and transmission of gametes.[10,11] The testicles are the primary male reproductive organs enclosed by the tunica albuginea capsule in the testicle sack. Two morphologically and functionally separated parts are in the testis. Tubular components include seminiferous tubules and intercellular portions between seminiferous tubules. The intertubular portions of the seminiferous tubules are involved in providing blood and immune responses.[12–14] Leydig cells are one of the most important cells in testis that are the source of testicular testosterone and insulin-like factor 3. In addition to Leydig cells, intercellular components include immune cells, lymphatic and blood vessels, nerves, connective tissue, and fibroblasts.[15–18] The seminiferous tubules are functional units in the testis, accounting for 60–80 percent of testicular volume.[19–21] These tubes are surround by epithelial tissue and include two types of cells: Sertoli cells and spermatogenic cells. The function of Sertoli cells is to nourish and develop sperm through the stages of spermatogenesis and their mechanical support.[22–24] These cells produce two types of inhibin and activin hormone that have positive and negative feedback to FSH.[25–27] In addition, Sertoli cells control the stages of sperm release into the lumen, phagocytosis of the degraded germ cells and additional cytoplasm resulting from sperm release. In adulthood, Sertoli cells are meiotically inactive.[28–30] Sertoli cell division terminates concurrently with the first meiotic division of the germ cells, giving rise to tight junctions between these cells, known as the Blood-Testis Barrier (BTB) (Figure 2).[31,32] The epithelium of seminiferous tubules is divided into two (functionally different) regions by BTB. Two important functions for BTB are: (a) the physical separation of the germ cells that protect them against the immune system; (b) providing an environment for meiosis and sperm development.[33–35]

Spermatogenesis

Spermatogenesis is one of the most crucial stages in male fertility.[36–39] The slightest deviation from the natural course

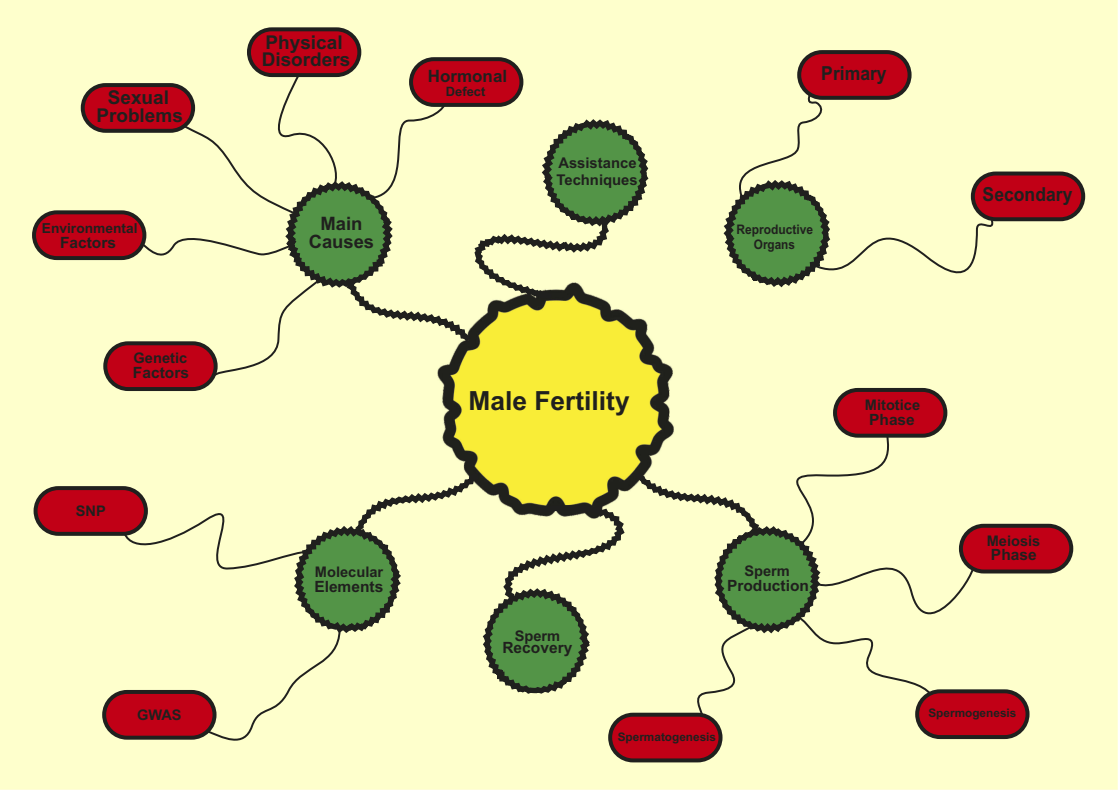

Figure 1 Main factors involved in male infertility.

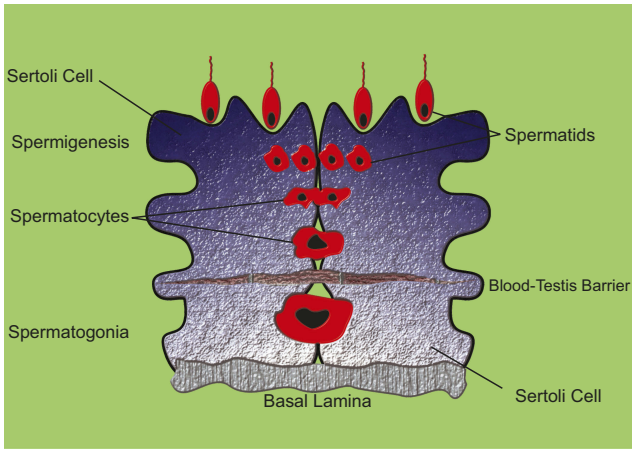

Figure 2 Schematic of the Blood-Testis Barrier.

of spermatogenesis can lead to infertility in men. The term spermatogenesis is a description of the development of male gametes in the seminiferous epithelial tissue from diploid spermatogonia that results in the release of differentiated haploid germ cells into the seminiferous tubules. Each cycle of spermatogenesis in humans requires 16 days and almost 4.6 cycles for development and differentiation of spermatogenic cells into adult sperm, which takes approximately 74 days in humans.[40–42] The regulation of spermatogenesis occurs in two main stages: a) hormonal and endocrine b) paracrine and autocrine. Many studies have shown that testosterone and FSH are required to successfully complete spermatogenesis.[22,43] The spermatogenesis process divided into four general phases: 1) mitotic proliferation and spermatogonial differentiation into pre-leptotene spermatocytes (spermatogoniogenesis); 2) Meiotic division of spermatocytes that leads to spermatids (meiosis); 3) Conversion of round spermatids into adult spermatids (spermogenesis); 4) Release of elongated spermatids into the lumen (spermatogenesis) (Figure 3).[44] Considering the importance of spermatogenesis and since the disorder at any of its stages can have irreversible consequences, below are some of the most important features of each stage.

Spermatogoniogenesis

The germ cell lines originate from the primary germ cell (PGC).[45] In humans, PGCs develop between endoderm cells at the end of the third week of development, and by the fifth week they migrate to the genital tract, where the presence of the Y chromosome results in the proliferation and transformation of the genital tract into primary male sexual organs.[46–48] PGCs are commonly called gonocytes during the first trimester of mitosis, then stop in the G3 phase of the cell cycle and remain silent until birth (i.e., when they become spermatogonia).[49–51] Spermatogonia remain silent until puberty. Spermatogenesis begins with the mitotic proliferation of spermatogonia after birth.[52–54]

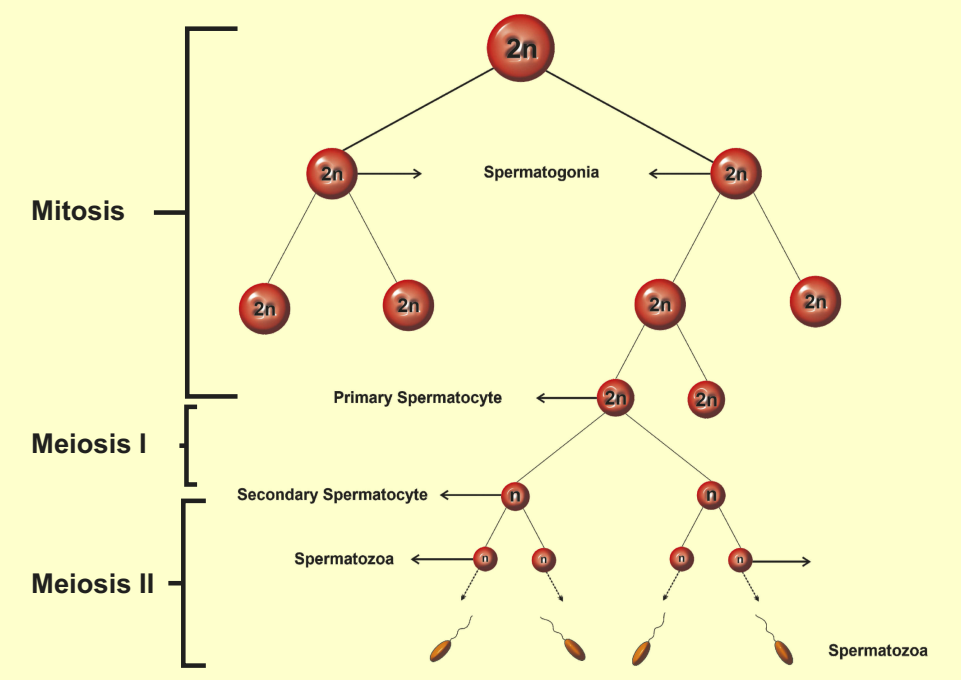

Figure 3 Spermatogenesis process.

Spermatogenesis during puberty is probably initiated by the production of bone morphogenetic protein 8B (BMP8B). Mice with lack of Bmp8b do not initiate spermatogenesis at puberty and consequently are infertile.[55–57] Two distinct fates await reproductive cells: (a) self-renewal by replication; (b) becomes spermatozoa. Apoptosis in spermatogonia rarely occurs in the human seminiferous epithelial tissue, but the rate of apoptosis is increased in patients with impaired spermatogenesis, especially in spermatocytes and spermatids.[58,59]

Meiotic Division

Meiosis is the distinction between sexual reproduction and non-sexual reproduction.[60,61] Meiosis eventually results in the production of haploid gametes from diploid cells. During mammalian meiosis, nuclear division is done twice in a cycle of DNA replication. Each meiosis division is generally divided into two stages Meiosis I and Meiosis II.[62–64] In meiosis I, also called subtractive division, the microtubules are attached to sister chromatids via the kinetochore and transported to opposite poles.[65–67] This transition leads to a decrease in the number of chromosomes from diploid to haploid. Meiosis II is an equal division, in which the microtubules attach to the kinetochore of centromere and separate the sister chromatids, resulting in the formation of four daughter haploid cells. Meiosis begins with the production of two pre-leptotene spermatocytes from spermatogonia. In meiosis I, primary spermatocytes become two secondary spermatocytes, and these cells then form spermatids in meiosis II. The result of meiosis is four different (genetically) cell types.[68–70]

Spermogenesis

Spermogenesis is a process that transforms the meiosis II final product (i.e., spherical spermatids) without splitting into specialized elongated spermatids. This process requires the development of the cytoplasm and nucleus regeneration, which can comprise four distinct phases: the Golgi phase, the capping phase, the acrosomal phase, and the maturation phase.[71–73]

Spermatogenesis

Sperm production is the final stage of spermatogenesis, which mature spermatids are released from the somatic supporting Sertoli cells into the lumen of the seminiferous tubules. At this stage, the cells are known as spermatozoa and continue their journey to epididymis. Seminiferous spermatozoa have low motility and fertility. Spermatozoa passage through the epididymal duct is crucial for final maturation and ability to move.[74–76] A small amount of cytoplasmic content, cytoplasmic droplets remain in the neck region and the middle segment of the spermatozoa, which facilitates the achievement of epididymis. During the transition from epididymis, which takes approximately two weeks, the cytoplasmic droplets move and exit during the spermatozoa tail, which is associated with increased spermatozoa movement. This event is associated with an increase in the movement of spermatozoa.[77–79]

Main Causes of Infertility

As mentioned, infertility can have a feminine or masculine origin, with the male factor only present in one third of cases. The diagnosis of infertility in men is mainly based on semen analysis. Unusual parameters of semen include: sperm concentration, appearance and motility.[80,81] There are seven main cases of semen-related abnormalities. Infertility in men can be due to a variety of causes, however, in almost 40% of infertile men there is no clear etiology. There are various reasons for male infertility, the most important of which are: Hormonal deficits, physical causes, sexually transmitted problems, environment and lifestyle, and genetic factors.[82–85]

Hormonal Defects

The male reproductive hormone axis is known as the hypothalamic-pituitary-gonadal axis. It consists of 3 major components: the hypothalamic, pituitary and testicular glands (Figure 4).[86,87] This axis works very regularly to provide the right concentration of hormones for male sexual development and function. Any abnormality in the system can lead to infertility.[88–90] If the brain is unable to produce gonadotropic releasing hormone (GnRH), this disorder results in a lack of testosterone and stopping sperm production.[91,92] Lack of GnRH causes a group of disorders known as hypogonadotropic hypogonadism.[93,94] One of them is known as Kallmann syndrome, which is associated with a change in sense of smell and immaturity.[95] Treatment options for gonadotropin-releasing hormone deficiency include: Use of sex steroids, gonadotropins and injection of gonadotropin releasing hormone. Testosterone injections are mainly used to improve testicular growth, normalize testosterone concentration, and stimulate the development of secondary sexual traits.[96–98] Similarly, the pituitary's inability to produce sufficient amounts of luteinizing hormone and follicular stimulating hormone results in a failure to stimulate the testes and to produce testosterone and

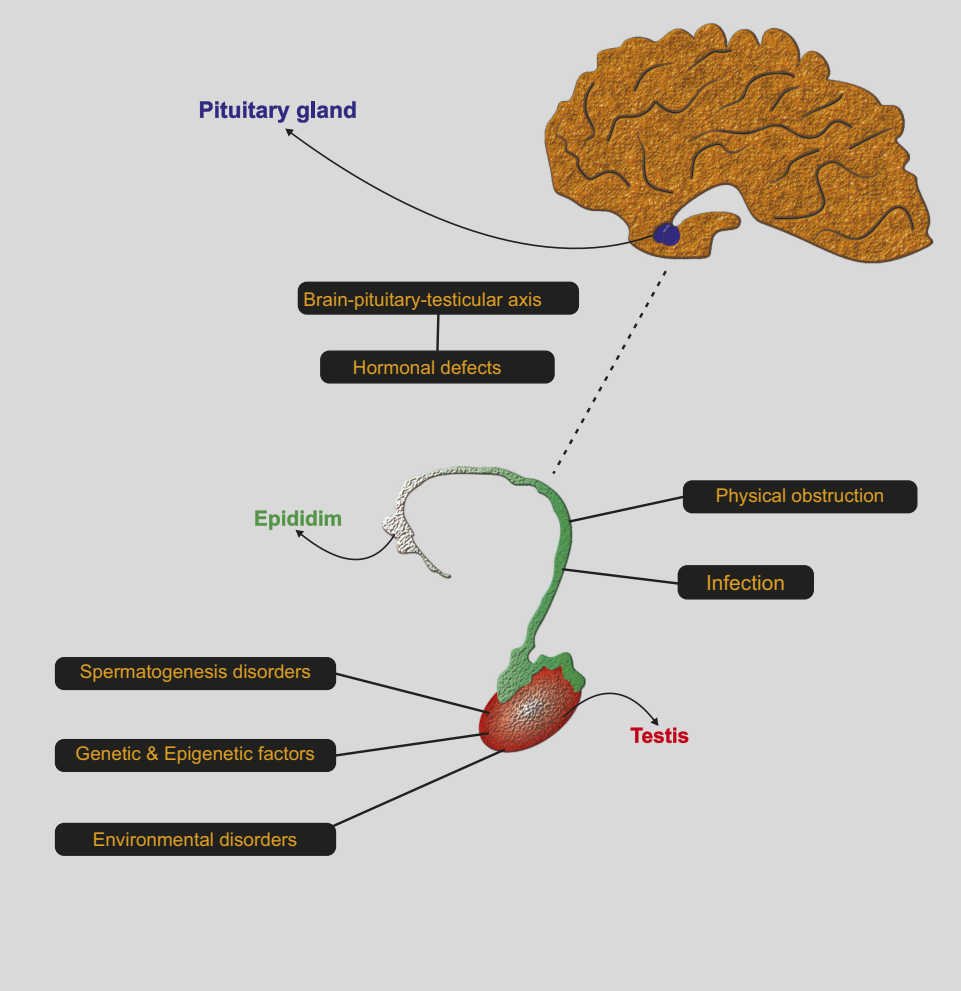

Figure 4 Brain-pituitary-testicular axis.

sperm.[99,100] Patients with pituitary deficiency require long-term hormonal therapy, which can lead to complications such as diabetes mellitus, heart disease and bone defects. Conversely, elevated concentrations of LH and FSH are associated with low concentrations of testosterone, leading to defects in spermatogenesis.[101,102] Therefore, using high doses of testosterone and estrogen can be a viable treatment option because it suppresses the production of LH and FSH. Increased prolactin can also lead to reduced sperm production, libido and impotence. Hyperprolactemia leads to infertility in 11% of people with oligospermia.[103] In many cases, a dopamine agonist can be a good treatment.

Physical Reasons

Physical problems can disrupt sperm production and blockage of the ejaculatory pathway. Enlargement of the sperm vessels known as varicocele is one of the most common male infertility problems affecting about 40% of men.[104,105] Testicular torsion within the testicle sac can cause testicular damage due to pressure on the sperm vessels and impaired testicular circulation. Chronic and acute genital tract infections can also be common causes of infertility in men.[106] Mumps viral infection can lead to testicular atrophy and infertility.[107] Sexually transmitted diseases such as Gonorrhea and Chlamydia can also lead to infertility in men due to obstruction in the epididymis.[108] In some cases, semen is ejaculated in the bladder, known as recurrent ejaculation, and accounts for about 2% of infertility cases that can be caused by anatomical problems of the bladder sphincter.[109]

Sexual Problems

Many sexual problems are both physical and psychological. Erectile dysfunction, known as impotence, early ejaculation and inability to ejaculate are examples of intercourse problems.[110,111]

Environment and Lifestyle

Men exposed to hazardous substances in their workplace, including solvents, insecticides, adhesives, silicones and radiation, exposure to these and similar substances can lead to infertility.[82,112,113] Exposure to radiation can lead to reduced sperm production, and exposure to high doses can lead to complete infertility. Overuse of the sun bath can also lead to a temporary decrease in sperm count.[114] Occupations that require prolonged sitting (such as driving) or being exposed to high temperatures (such as bakeries) can have negative effects on fertility.[115] Concerning alcohol consumption and smoking, there is no definite agreement regarding their effect on sperm parameters and fertility outcomes.[116,117] However, progressive degradation in sperm quality may be associated with cigarette smoking and alcohol consumption. Poor nutrition can also play an important role in male infertility. There has been a recent report of a decrease in sperm concentration in men with an increase in saturated fat intake.[118] Repeated use of drugs such as cocaine and cannabinoids is associated with a significant decrease in sperm concentration, and urinary testosterone in men.[119] In addition, studies have also shown that air pollution in men reduces sperm motility, and the way to deal with and prevent this problem is to continually use antioxidants and vitamin C-containing substances. Moreover the presence of pollutants and sulfur dioxide in the air changes the natural shape of sperm and also has a detrimental effect on sperm motility.[120–123]

Genetic Factors

Genetic factors are detected in 15% of male infertility cases and can be classified into two groups: chromosomal abnormalities and single-gene mutations.[124,125] Any lack or acquisition of unusual rearrangements in genetic material at the chromosomal level is known as chromosomal abnormalities and is one of the major genetic causes involved in male infertility.[126] About 14% of men with azoospermia and 2% of men with oligospermia have chromosomal abnormalities, which is much higher than the general population (about 0.6%).[127,128] Some chromosomal abnormalities are inherited and some are acquired. The most common genetic cause of azoospermia in the aneuploid sex chromosome is Klinefelter syndrome, which accounts for about 14% of male infertility cases. 47,XYY, chromosomal defects can cause spermatogenesis malfunction due to increased FSH and Y chromosome disomy.[129,130] Noonan syndrome in men, such as Turner syndrome in women, which is XO/XY mosaic, can lead to cryptocidism and spermatogenesis deficiency due to increased FSH.[131,132] Translocations occur in 3% of patients with severe oligozoospermia, the most important is Robertsonian and bilateral translocation.[133,134] Inversion is called chromosomal translocation, in which a fragment of the chromosome is broken and rearrangement within itself.[135] Autosomal inversions are eight times more frequent in infertile men,[136] although these rearrangements are balanced, in some cases leading to severe oligoasthenoteratozoospermia or azoospermia.[137] The role of the Y chromosome was identified by Zofardi and colleagues by karyotype analysis of deletions in the long arm of the Y chromosome in six infertile men, they termed the deletion region as azoospermic factor (AZF).[138] This region contains three zones AZFa, AZFb, and AZFc.[139] Micro-deletions occur following the recombination of similar fragments in palindromic sequences. Y chromosome microdeletions are present in 10% of infertile men, whereas in oligozoospermic males, the prevalence is 7%.[140,141] The most common microdeletion occurs in the AZFc region, accounting for 80% of cases.[142] Deletions that encompass the entire AZFa region result in the Sertoli cell phenotype.[139] Intra-AZFb deletion usually results in azoospermia.[143] Deletion in the AZFc region can lead to a wide range of infertility phenotypes including azoospermia, Sertoli cell syndrome and oligozoospermia.[144] Some gene mutations with pathological syndromes can be associated with infertility, such as congenital bilateral absence of the vas deferens (CBAVD), which cause obstructive azoospermia in 80 to 90% of cases.[145] This defect is caused by a mutation in the Cystic fibrosis transmembrane regulator (CFTR).[146] Primary ciliary defects are an autosomal recessive heterogeneous defect caused by a lack of normal eyelash function and present in half of men with asthenospermia. Little has been known so far about non-syndromic infertility.[147]

Epigenetic Factor

Acetylation and methylation are two effective factors in epigenetic modifications that cause different expression of genes. Epigenetic factors act a critical role in male infertility, and numerous studies have been devoted to it. During spermatogenesis, germ cells face major epigenetic reprogramming that includes the organization of sex-specific designs in the sperm, which substitution of histone to protamine is one of them.[148–150] Numerous experiments have revealed altered epigenetic function in sperm from men with oligozoospermia and oligoasthenoteratozoospermia. Besides, many studies have been reported that

hypermethylation in several genes, lead to deficiency in semen parameters or male infertility.[151–153]

Strategies for Finding Genes Involved in Infertility

There are two general approaches to infertility studies for finding genes involved in infertility: the candidate gene approach and the whole genome approach. A) The candidate gene approach; Identification of genes that lead to impaired fertility in model animals (mostly mice), and assuming that their function is maintained during evolution, these genes are selected and their roles and effects in human infertility are studied. It is important to note that in this method, the function and expression of candidate genes in model animals and their effect on infertility have already been proven, and given the foregoing, it is possible to predict the gene involved in human infertility. B) Whole-genome approach; technological advances in whole-genome studies such as single-nucleotide polymorphism (SNP) microarray, high-throughput sequencing technologies such as exome or whole-genome sequencing, and their use for finding effective genes in infertility has been considered.[154,155] In single nucleotide polymorphisms or SNPs, the difference in one nucleotide causes different phenotypes. SNPs are classified into common and non-common groups based on allele frequency. Sequencing technologies enable researchers to perform high-throughput sequencing, which allows millions of pieces of DNA to be sequenced. Exome sequencing is another field that has revolutionized the study of a variety of disorders, including infertility. Exom covers about 1% of the entire human genome but accounts for about 85% of the pathogenic mutations.[156] Exome sequencing allows us to identify mutations in the protein coding region. On the other hand, whole-genome sequencing can identify potentially susceptible mutations throughout the genome. Genome-wide association studies (GWAS) have been able to identify different polymorphisms related to defects in spermatogenesis. Until now, however, genetic risk factors identified with this technique have shown poor association.

After introducing some of the influencing factors in infertility and exploring its identification methods, the challenge that remains to be resolved is how to use the information obtained to treat diagnosed infertility. Following some of the most up-to-date and important strategies for treating infertility with a specific cause, are mentioned.

Fertility Assistance Techniques

Although different definitions have been proposed, assisted reproductive techniques refer to a range of methods generally used to treat infertility problems in humans and help infertile couples to have a healthy child. There are three main stages of progressive intervention in this area. A) Stimulation of ovulation during intercourse. B) Stimulation of ovulation and injection of sperm into the female reproductive tract. C) Artificial fertilization in which the egg and sperm are fertilized outside the body and the resulting embryo is transferred into the uterus. Each of these steps is discussed below.

Auxiliary Fertilization

This process involves controlled ovarian stimulation to increase the maturation of several oocytes, egg harvest through follicle aspiration, sperm recovery, laboratory inoculation, and embryo transfer and culture. Although assistant fertilization can be performed in the normal sex cycle, the most common protocol involves the daily injection of recombinant human FSH to stimulate follicle growth to obtain the most oocytes.[157,158] The follicles are monitored by serum estradiol and uterine ultrasound. Once the follicles have reached the appropriate size, human chorionic gonadotropin (HCG) is injected to stimulate follicle maturation and is collected 32 to 36 hrs after injection. Although frozen sperm can also be used according to WHO guidelines; Generally, on the day that eggs are collected, semen is also collected by masturbation after a period of 2 to 7 days of abstinence for artificial insemination, After egg stimulation and sperm recovery, two methods of fertilization are used: IVF and ICSI.[159,160]

Sperm Recovery in Infertile Men

For infertile men, sperm must be recovered directly from the testicles or epididymis. Obstructive azoospermia (OA) and non-obstructive azoospermia[51] are two major categories of azoospermia.[161] Obstructive azoospermia is the result of physical obstruction of the male genital tract, which may be due to or acquired factors (i.e., infection, vasectomy or physical injury to the genital tract), congenital absence of the vas deferens (congestion of the vas deferens, which accounts for about 60% of men with azoospermia), epididymal obstruction.[162] On the other hand, NOA is due to the lack of testicular sperm production in the ejaculate.[163,164] The best way to treat NOAs is to extract sperm from the testis (TESE) and done

intracytoplasmic sperm injection (ICSI). However, in half of the cases of azoospermia, sperm cannot be found as a result of TESE.[165] Unfortunately, serum hormone levels such as FSH and inhibin B and noninvasive assessments such as testicular volume cannot predict sperm recovery and to date only testicular histopathology can be used as a predictor of successful sperm recovery rate (SSR).[166] In the conventional TESE method, spermatozoa are extracted from testicular biopsies by local or general anesthesia.[167] On the other hand, sperm extraction is much safer and more successful by micro-TESE.[168]

The purpose of the micro-TESE is to identify the nuclear regions of testicular sperm production based on the size and appearance seminiferous tubules with the aid of a microscope, in which spermatozoa can be recovered from open seminiferous tubules, the whole process being visible under the microscope. Micro-TESE is a better alternative to TESE because of the increased chance of sperm recovery and reduced testicular damage due to the smaller size of the harvested tissue. In general, testicular tissue resection for histopathologic evaluation can potentially eliminate sites that still produce sperm, despite abnormalities.[169,170] Testis biopsy before sperm recovery is generally not recommended. Testicular biopsy is usually performed on the day of egg retrieval. Biopsy specimens are examined for the presence of sperm. A small sample is taken from an accessible area and evaluated for histopathology.[170–172] Due to the uncertainty of sperm retrieval and failure of sperm retrieval, egg retrieval will be unnecessary. This can cause emotional, economic, and physical stress for couples, so sperm retrieval requires the use of predictive factors, and this will not be possible unless you have in-depth knowledge of all the steps that can lead to Infertility in men.

Discussion

Today, around 10–15% of couples around the world are experiencing infertility (60–80 million people). In half of cases, male infertility is the cause. Disruption of spermatogenesis is a major cause of infertility, and genetic abnormalities affecting spermatogenesis can be the cause of many unknown male infertility cases. Therefore, identifying and presenting prognostic biomarkers as well as finding non-invasive therapeutic techniques seem necessary. In hormonal investigations, the micro-TESE technique can increase the biomarker value of FSH to predict sperm recovery; because the results of hormonal studies show the whole process of spermatogenesis in all areas of the testis. Given that the testicular tissue is heterogeneous, the micro-TESE technique can increase the likelihood of sperm retrieval despite inadequate levels of the FSH hormone, due to sampling small areas of testicular tissue.

Conclusion

Given that male infertility in many cases remains unknown. Therefore, it is necessary to introduce new key factors and diagnostic and noninvasive biomarkers. Over the past few years, the identification and evaluation of small noncoding RNAs in many diseases, including infertility, has helped greatly in understanding the underlying mechanisms of disease. But this alone is not enough, and through increased insight into the complex stages and processes of pregnancy in humans, more key elements must be identified so that infertile couples can enjoy the chance of a natural pregnancy in addition to reducing costs and problems. With the advances in technology and the introduction of new methods and approaches, it is hoped that many of the causes of male infertility will soon be identified and treated.

Abbreviations

BTB, Blood-Testis Barrier; PGC, primary germ cell; GnRH, gonadotropic releasing hormone; AZF, azoospermic factor; CBAVD, congenital bilateral absence of the vas deferens; CFTR, cystic fibrosis transmembrane regulator; SNP, single-nucleotide polymorphism; GWAS, genome-wide association studies; HCG, human chorionic gonadotropin; OA, obstructive azoospermia; NOA, non-obstructive azoospermia; TESE, testicular sperm extraction; ICSI, intracytoplasmic sperm injection; SSR, sperm recovery rate.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no conflicts of interest.

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