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Male Infertility: Etiological Factors [A Review]

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Abstract: In recent decades, the incidence of infertility has increased both in developed and developing countries either due to increase in environmental or social pollutions. Infertility creates serious social and psychological problems. There are various exogenous and endogenous factors that seriously compromise male fertility. This review focuses in detail about male infertility andit'sassociated various etiological factors.

Key words: Endogenous · Etiology · Exogenous · Infertility · Pollution

INTRODUCTION

Reproduction is an extremely important event in human's life. It is strongly linked with the ultimate goal of happiness, completeness and family consolidation [1]. Successful reproduction is one of the significant steps for fertility outcome in humans. Fertility is the capability of an individual to induce or conceive pregnancy within one year of unprotected intercourse [2]. While, infertility is the inability of individuals to establish pregnancy, in spite of regular and unfortified intercourse [3]. There are mainly two types of infertility. Primary infertility denotes a situation in which couples have never given birth to children, whereas secondary infertility is defined as the condition in which couples are unable to give birth to children after twelve months of sexual intercourse (without any hindrance) following earlier conception and not using any contraceptive methods/medications [4]. Infertility is a multi-dimensional problem with socioeconomic and cultural consequences. Approximately 15% of all couples are affected by infertility [5], with an increasing anticipation over the next 20 years [6]. Idiopathic infertility is one of the most frequent types of male infertility, which is characterized by the presence of one or more abnormal semen characteristics with unknown etiology [7].

Mechanism of Spermatogensis and Ejaculation: Spermatogenesis (sperm production) is a continuous complex biochemical process. Sperm can be found in the testis at different stages of their development. The germ cells (in men, these are the cells in the testes that develop to produce immature sperm cells) take 70 days to grow up into a fully developed sperm found in seminal fluid that may fertilize an egg. It means that when the sperm is released from the testis today started their development weeks before. The repeated division of germ cell in the linings of seminiferous tubules results in the development of sperm. The process of spermatogenesis starts from the spermatogonium. These dividing cells go through several developmental stages that lead to a spermatid (round cell) to the 'tadpole-like' sperm. At the final developmental stage, sperm are passing out from the seminiferous tubules and released from testes into the epididymis. When the process of ejaculation starts, sperm are carried out due to waves created by muscular contractions, with a minute amount of liquid from the epididymis via the vas deferens. The vas deferens at the back of bladder becomes the ejaculatory ducts, passing through the prostate gland to join the urinary tract, via entering the prostatic urethra (the section of the urethra that is located in the center of the prostate) [8].

Sperm Morphology: Sperms are submicroscopic (0.05 millimeters long) male reproductive cells. Fully developed sperm cells are very specialized and are composed of three different segments, the head, neck and tail. In the head nucleus is found, which consists of twenty three chromosomes. The head part is designed in such a way that helps in attachment and penetration into

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the female egg. The head part of the sperm is connected to the tail though the neck. The mitochondria are situated at the part of the tail nearest to the neck, providing energy for the sperm movement. The whipping motion of the tail pushes the sperm towards the egg.

The sperms are mixed in the prostatic urethra with the fluid from the prostate gland. Additional fluid enters the urethra through the ejaculatory channel from the seminal vesicles. The greasy fluid made by the Cowper's glands further helps the passage of fluid along the urethra. The fluid mixture from the testes and other secondary sex glands, move along the penile urethra (the section of the urethra located in the penis) to the external tip of the male sex organ and is released at the time of sexual intercourse.

The epididymis is a long, highly-coiled tube leading from each testis, is situated at the back of the testes which connects the seminiferous tubules to the vas deferens. The sperm spend two to ten days travelling via the epididymis when released from the testes. During this trip, the sperm matures and become motile (swim or move). At the advent of ejaculation, sperms are passed from the end of the epididymis, through the vas deferens, to the urinary tract (urethra) in the male sex organ. For accomplishing pregnancy, sperm must be entering into the vagina at the fertile days of a woman's menstrual cycle. Sperms then must move through the woman's uterus (sometimes called the 'womb') and into the uterine tubes where they meet the egg. Fertilization of the egg happens when moving sperm attach to and then enter the egg [9].

Role of Hormones in Controlling Spermatogenesis: During the early stages of puberty, the level of LH and FSH rises, the testes grow up and mature under their influence. The male sex hormone, testosterone is made up in the Leydig cells of the testes with the help of LH. Testosterone is the main androgen hormone required for the growth and differentiation of secondary sexual characteristics, physical changes, genital development and facial body hair growth in young boys at puberty. Testosterone along with FSH regulates spermatogenesis in the seminiferous tubules of the testes [10].

Etiology of Male Infertitly: Male infertility may be caused by various factors including medical (acquired or genetic), environmental exposure to different agents (chemicals, chemotherapeutic agents, radiations, pollution and stress) and life style habits (smoking, alcohol use, illegal recreational drugs use). Male infertility is divided into two major groups for example, Primary infertility: when a male have never had fathered a child. Secondary Infertility is described as the condition when a male fails to become a father after having had offspring's previously.

Male factor is considered as a major contributory element to infertility and responsible for approximately 50% of the infertility cases [5]. Infertility in male is mainly caused by deficient sperm concentration, decreased sperm viability, reduced semen total volume and abnormality in the morphology of the sperm [11]. Moreover, there are other risk factors responsible for defective spermatogenesis and male infertility, including cryptorchidism, obstructive lesions, varicocele, ejaculatory problems, genitourinary tract infections (bacterial as well as protozoa), accident, cystic fibrosis, genetic complications, environmental factors, disturbances, immunological factors, oxidative stress, nutritional deficiencies of the trace elements, fructose level and vitamins etc. [12-13].

In addition, the etiology of infertility includes anomalies in any part of the reproductive system [14]. Abnormalities of the testes include acquired, congenital or unknown disorders leading to spermatogenic arrest. Testicular congenital causes include cryptorchidism (testicular dysgenesis), anorchia, Y chromosome deletions, Sertoli cells only syndrome and sperm cells maturation arrest. Testicular causes of infertility which are acquired include accident, torsion, medicines, radiations (x-rays), orchitis, surgical procedures, systemic infections (hepatic or liver failure), Sexually transmitted diseases (AIDS, gonorrhea, Chlamydia) and varicocele. Causes of post-testicular infertility comprises blockage of the ejaculatory ducts which result in the defective transportation of spermatozoa form the testes. These defects may be acquired due to surgical procedures (vasectomy) or congenital in nature by the absence of vas deference [14].

Environmental Factors Contributing to Male Infertility: Various environmental factors have also been documented to affect male infertility in human population. Air Pollution The release of unwanted pollutants into the air is called air pollution. The air in the atmospheres is naturally clean. It is contaminated by different pollutants of man-made resources including pollutants from various sources like motor vehicle smoke, industrial releases and the burning of wood and coal etc. These pollutants include emissions including, CO, NO_2, SO_2 and O3 into the air [15-16].Though air pollution has received great consideration in the last several years for issues related to

health, its effects on fertility are not well-documented. Several reports pointed out the impact of air pollution on male fertility. Studies in Czech Republic regarding male fertility was carried out on two groups of males living in two separate locations, one group were highly exposed to pollution [17].Those who were affected by high amount of pollution in the air were more prone to experiencing abnormalities in semen parameters. Significantly negative association was also noted between sperm count and the degree of exposure to ozone [18].

Pesticides and Other Chemicals: There are many chemical substances which are abundantly used nowadays in many ways. Some of these are pesticides and chemicals that are disrupting the endocrine system and greatly impact the reproductive health, resulting in complications of both male and female fertility. These chemical substances disturb the natural body hormones, impeding their synthesis and normal activity influencing the reproductive capability of the body [19]. There are several studies conducted on the negative effects of various chemicals on reproductive health [19-20].

Radiations: Different types of radiations are widely used now days for various purposes in the treatment of cancer and many research procedures. The time and amount of exposure to various types of radiations can have ever lasting effects on humans. Especially x-rays and gamma rays have lethal effects on the germinal and Leydig cells in the human body. These radiations ultimately can result in permanent damage resulting in sterility [21-22].

There have been a lot number of studies on the use of mobile phones representing negative effects on fertility[23], viability and increasing ROS (reactive oxygen Species) [24], decreasing sperm count and increasing abnormalities in sperm morphology[23].

Exposure to Chemotherapeutic Agents: It is well known that cancer treatments adversely affect male fertility. Treatment of cancer by chemotherapy and radiotherapy cause short term or permanent gonadal dysfunction and cytotoxic effects in male patients. Such type of treatment procedures has a negative impact on male capability to have biologic offspring at child bearing age [25].

The extent of spermatogenesis loss is based on the reality that the dividing sperm cells are highly sensitive to the killing effect of cytotoxic chemotherapeutic agents and radiations [26], so the biological mechanism of sperm production remains fixed and unaffected after chemotherapy. Decrease in sperm count occurs from the cytotoxic adverse effects of chemotherapy or due to radiotherapy treatment upon the spermatogenic epithelium. Though, if the epithelium of the spermatozoa survives, there is a risk of hazards to reproduction because cancer treatment produces mutagenic effects on sperm. Experimental studies on animal show that there is Tran's generational expression as a diversity of effects ranging from miscarriage to carcinogenesis because of the presence of DNA damage in the male genome. It has been established for many years that radio and chemotherapy treatments adversely disturb the germinal epithelium in the testes of pre-pubertal and adult male[25]. Male patients suffering from cancer, develop gradual fall in sperm function due to ejaculatory problems as a result of radiotherapy or chemotherapy [27].

Human reproduction is a highly sensitive biological process and is adversely affected by cancer and its chemotherapy which cause disruption of reproductive capability in both male and female. Though in case of successful conception after cancer diagnosis and chemotherapy, there are worries about the possibility of adverse effects on perinatal and obstetric. In addition, chemotherapy and radiotherapy induce genetic defects in germ cells in children born of cancer patients due to deformities and chromosomal abnormalities [28].

Life Style Factors Effecting Male Infertility

Nutrition: Balance diet is essential for maintaining good health. For proper functions of the body systems, food should contain all the essential vitamins, carbohydrates, proteins and trace elements that might have a bitter impact on reproductive physiology of the human. Healthy diet has a good influence on fertility. Good quality of semen is positively correlated by using food having abundant foliate, carbohydrates, lycopene and fiber[29], as well as fruit and vegetables [30].

It is useful to eat lesser amount of both proteins as well as fats for maintaining fertility [29]. The main role of antioxidants is to remove the ROS in the seminal fluid and help in the conversion of reactive oxygen species to a more beneficial product for the cells. Oxidative stress developed as a result of excessive ROS can impact on the protein contents of the sperm, lipid and breakdown of sperm DNA and sperm male function [31].

Smoking: According to WHO report, cigarette smoking is injurious to health because it is the leading cause of lungs and cardiovascular diseases in human. Cigarette contains tobacco and around 4,000 chemical compounds are produced during the combustion of tobacco. The main

constituent in the particulate part of tobacco is composed of nicotine, whereas the gases produced during the burning of tobacco contains carbon monoxide, ammonia, hydrocarbons and nitrogen oxide. Polycyclic aromatic hydrocarbons are responsible for the activation of a pro-apoptotic protein in mice [32], which confer damage to the zygote and impact fertility. Smoke of cigarettes contains more than 30 different chemical compounds which are known to be carcinogenic, mutagenic and aneugenic and has known lethal effects on human embryos and germ cells [33].

Cigarette smoking is related to a number of potential health problems. The incident of smoking in males at their reproductive age is 35%. Those men who are smoking while planning for producing offspring, decreasing their fertility potentials in contrast to non-smokers [34]. It is ascertained that men who smoke incline to have a decrease in semen volume [35], sperm concentration, [36], progressive motility [35, 37], normal sperm morphology [37] and fertilizing capability [38]. Calogero *et al*. established from their study that smoking could lead to a decreased fertilization capacity by reduction in the mitochondrial activity in spermatozoa [35]. According to the report of Guar *et al*. both moderate and heavy smokers in their study exhibited abnormalities in sperm motility, count and morphology (astheno-, oligo- and teratozoospermia). Damageto DNA integrity of the sperm is also caused by smoking [33, 35]. It has been reported that smoking disrupts endocrine function, increases in serum levels of both LH and FSH and decreases in serum testosterone [39].

Stress: It is well known that living and working in this modern society where needs are many fold impeding one's life full of stress. It affects our society in all fields of life. Infertility problem is also a stressful situation, owing to pressures from the society, investigation procedures, treatment failure, unsatisfied diagnostic test results, un accomplished tasks, frustrated desires and even associated economic costs [40].

Drugs (Gonadotoxins): The drugs used in cancer chemotherapy cause adverse effects on the testicular germinal epithelium and interfere with cell division and damage the Leydig cells. The nature of effects differs with the type of drug, dose and patient age [41].

Cimetidine is one of the most commonly administered drugs known to be an androgen competitor [42]. Studies reveal that all those men who are treated with cimetidine present with gynecomastia and may have sperm abnormalities [42-43].

Medical Causes of Male Infertility: Large numbers of clinical complications are also involved in male infertility. Some of them are discussed below.

Weight: Eating habit and amount of physical activity is often associated with an individual's weight. BMI (Body mass index) is documented as a number for the body weight. Health status is significantly affected by Body weight, the leading cause of cardiovascular diseases, diabetes and infertility [44].

Obesity: Obesity is a medical condition which is the most important characteristic of metabolic syndrome. It adversely affects male fertility through several pathways. First, it happens due to the conversion of serum testosterone in the peripheral tissues in to high concentration of estrogen in adipose tissue which results in secondary hypogonadism via inhibition of hypothalamic-pituitary-gonadal axis. Development of oxidative stress in the testes results in reduced spermatogenesis and high sperm structural damage. Finally, high temperature in the scrotum in severely obese men is developed due to the accumulation of more fats in suprapubic and inner thigh which induce fertility complications[45].

Erectile dysfunction (ED) and obesity is positively correlated. According to the report of Corona *et al*. 96.5% of the men with metabolic syndrome have complain of ED [46]. ED is caused by the conversion of androgens to estradiol catalyzed by the enzyme aromatase, which is found mainly in adipose tissue [47]. With the increase in the amount of adipose tissue, more aromatase is available for the conversion of androgens, resulting in high estradiol levels in the body [47].

Diabetes: Diabetes mellitus (DM) is a metabolic disease characterized by diminished control of glucose metabolism resulting in high sugar level in the body (hyperglycemia). Both kinds of diabetes are well predictable as one of the cause of male sexual dysfunction resulting in infertility [48].

Male patients suffering from type I and type II diabetes are more frequently presented with subfertility. Increased apoptosis signaling and the rate of DNA fragmentation on subcellular level, have a negative impact on fertilizing capability of spermatozoa. It has been documented from the earlier studies, that oxidative stress is linked with defective sperm motility and poor DNA integrity in germ cells of diabetic male patients. Still, the mechanism of underlying pathophysiology of diabetes-related male subfertility is not fully understood until now [49].

Diabetes causes disturbance of sexual function through the following two mechanisms that is autonomic neuropathy and ejaculatory disorder with coexisting vascular diseases which are the major cause of erectile dysfunction (ED) in male. Among the diabetic patients, 35% to 75% of diabetic type 1 patients are affected by ED[50]and 40% of these patients suffer from ejaculatory disorders [51]. Ejaculatory dysfunction is demonstrated by slow and continuous decline in the amount of ejaculate-to-retrograde ejaculation to complete cessation of the ejaculate depending on the extent of concerned autonomic sympathetic neuropathy [51].

In addition, it is also documented that seminal volume has been reported to be decreased in patients suffering from diabetes (both types 1 and 2) as compared to normal men [48]. In summary, diabetes affects male reproductive function in various ways mainly the spermatogenesis by endocrine system, or by damaging the penile erection and ejaculation process.

Varicocele: The word varicocele was first time used by Curling in 1843 indicating the pathologic dilatation of veins of the spermatic cord [52]. In the early days varicocelectomy was done for relieving pain and improving cosmetics. In 1952 association between varicocele and infertility was recognized. According to a report of T.S. Tulloch of a man with testicular biopsy-having sperm maturation arrest, in which sperm count was improved after varicocelectomy[53].

Erectile Dysfunction (ED): It is considered that couples suffering from infertility develop stress due to unintentional childlessness. Stress interferes with spermatogenesis and fertility rate. The treatment procedures and expensive diagnostic test for long period may also have a negative influence on the sex life of the infertile couple. Higher frequencies of male sexual disturbances in the form of erectile dysfunction, ejaculatory disturbances, impotence and lack of sex drive in these patients have been documented in various studies [54].

Anti-Sperm Antibodies: Orchitis (inflammation of the testis) is characterized by the presence of specific antisperm antibodies (ASA)[55]. ASA have been found in approximately 10% of all infertile men as compared to fertile men (ASA 2%) [56]. The development of ASAs is related to unexplained male factor infertility.The data of Moghissi *et al*, [57] documented that the occurrence of sperm antibodies in patients with unexplained and persistent infertility was significantly higher (42.5%).The disorder of the blood-testis barrier [57] and defect in immuno-suppression [58], provoke the occurrence of antisperm immune responses. Vasectomy is considered as a major cause of ASA [58]. Amongst the other causes are varicocele, infection of the genital tract, homosexuality [59], testicular trauma, vas obstruction, torsion and malignancy [60]. The resultant ASAs can be detected in serum, seminal plasma and attached to spermatozoa. Amongst them, sperm-bound antibodies are clinically the most relevant antibodies including immunoglobulin G and IgA [3].

Orchitis is classified in to two groups. Primary autoimmune orchitis is demarcated by infertility and asymptomatic orchitis linked with ASAs (100%) focused to the seminiferous tubules in infertile men, without any symptoms and systemic diseases. Secondary autoimmune orchitis is associated with a systemic autoimmune disease and is characterized by orchitis (vasculitis). These patients complain of testicular pain and swelling or erythema. It is reported that 50% of the patients suffering from autoimmune orchitis have ASAs. The etiology of both types of orchitis is multi factorial still idiopathic. Studies demonstrate that ASAs cause interference with motility of the sperm and cause their agglutination, blocking sperm-egg interaction causing in infertility [61].

Congenital or Genetic Causes of Male Infertility

Y-Chromosomal Deletions: The human Y chromosome consists of approximately 60 mega bases and encodes 80 different proteins, some of which are involved in germ cell development and spermatogenesis [62]. In the AZFa region, USP9Y is useful active gene involved in spermatogenesisamong the gene family the main candidate gene is the RBMY (RNA binding motif) in the AZFb region, which has a restricted expression in the testis[63]. In male the AZFc region plays a vital role in fertility because it shows specific expression in the testis. Due to deletions in the AZFc regions 8% of the male are infertile, representing the most often deleted region in infertile men [64].

Klinefelter's Syndrome: It is the most frequent inherited cause of male infertility in humans, but many cases remain undiagnosed due to considerable changes in clinical presentation and insufficient awareness of professional. The spermatozoa from patients with Klinefelter's syndrome show higher frequency of sex chromosomal autosomal aneuploidies and hyperploidy than in those from a normal men. Therefore, in some cases chromosomal

errors might be transmitted to the offspring of men with klinefelter's syndrome. So the genetic consequences of the fertilization procedures must be elucidated to the patients and their partners with this syndrome [65].

Types of Male Infertility: Male infertility may be characterized into sub-groups based on abnormalities in the count and motility of spermatozoa in seminal ejaculate. Azoospermia is a condition in which there is no sperm and when there is sperm count < twenty million/ml "oligospermia". When the sperm count is normal and motility < fifty percent is known as asthenospermia", decreased percentage of morphologically normal sperm denotes teratospermia. The causes of male infertility can be diagnosed in nearly 70% of cases with help of related medical history, physical checkup, seminal and hormonal evaluation. On the basis of aetiology,azoospermia is divided into three primary categories: pretesticular, testicular and post testicular. The pretesticular and post-testicular causes of azoospermia are generally treatable, but testicular causes of azoospermia are not treatable. Endocrine abnormalities are the leading cause of pre testicular azoospermia characterized by deficient levels of androgens and altered gonadotropin levels. These abnormalities can be congenital (e.g., Kallmann syndrome), acquired (e.g., hypothalamic or pituitary disorders) or secondary (e.g., an adverse effect from a medication) [66]. Causes of testicular azoospermia include congenital, acquired or idiopathic disorders that result in spermatogenic failure. Congenital testicular causes include anorchia, cryptorchidism, genetic abnormalities, germ cell aplasia and sperm cells maturation arrest. Among the acquired testicular causes are infections, testicular tumours, medication, trauma, testicular tumours and exposure to irradiation, renal failure, surgery and varicocele. Obstructions of the ejaculatory ducts, which impair the transport of spermatozoa from the testis, are included in the post-testicular causes of azoospermia. These obstructions may be acquired because of infection or surgery (vasectomy) or congenital in nature caused by bilateral absence of the vas deferens (CBAVD) [66].

Male infertility may be classified due the defects related to the hypothalamus or pituitary gland, the testicles, or defective sperm transport because of the disorders in the penis and associated accessory sex glands. Infertile men with azoospermia and abnormal semen characteristics are observed, such as a deficient sperm count [67]. But it may also be caused by various aetiologies including congenital disorders such as congenital bilateral agenesis of the vas deferens (CBAVD). NOA is caused by defective spermatogenesis in the testis and can be classified into maturation arrest (MA), Sertoli cell-only syndrome (SCO, hypo-spermatogenesis (HP), according to the cell composition of the seminiferous tubules in the testes [6].

Endocrinology of essential reproductive hormones

For the evaluation and treatment of endocrine disorders understanding of reproductive physiology is essential. It is documented that an endocrinological cause of male infertility is rare (less than 2%), identification is important as precise hormonal analysis is often effective. These testicular functions are closely associated, because the synthesis of testosterone is not only required for spermatogenesis, but also for the development of normal sexual behavior and secondary sexual characteristics [42]. Kisspeptin, a neurohormone is a key regulator of fertility as its pulsatile secretion causes gonadotropin releasing hormone (GnRH) secretion which then acts on pituitary to secrete LH and FSH. This LH and FSH are then responsible for gametogenesis and steriodogenesis. Mutation in kisspeptin or its receptor can cause infertility [68-69].

Thyroid Function and Human Reproductive Health: For maintaining normal reproduction, normal thyroid function is essential because of its role in many pathways. Both thyrotoxicosis and hypothyroidism adversely affect male reproduction. Thyrotoxicosis causes abnormalities in sperm motility, while hypothyroidism is linked with abnormal sperm morphology [70].

CONCLUSION

Male infertility is the major factor responsible for fertility complications in infertile couples. As infertility is not the disorder of individual but the disorder of the couple. Therefore in infertile couples, male should be investigated first as there are various genetic, environmental and social factors that negatively affect fertility either directly or indirectly. Main factor for infertility is environmental pollutants which alter hormonal balance negatively. Susceptible infertile males should either avoid pollutants or use protective clothing during handling. Such infertile males should also avoid stress as stress decreases fertility indirectly by increasing cortisol and decreasing reproductive hormones. They should also focus on diet and exercise. Similarly, consanguineous marriages should be avoided in families having a family history of infertility.

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