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Review Article

A REVIEW ON COMMON FACTORS AFFECTING A SEMEN QUALITY OF MALE

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ABSTRACT

Reproductive disorder and infertility is emerging globally as serious medical and social problem. It is not just the women that need to be in good shape, men also need to be healthy and fertile to have the optimum chance of having an offspring. It is estimated that one of five couples are affected by some degree of infertility. Males are exposed to various factors which may decrease their reproductive capabilities. Hormonal imbalances, illness, reproductive anatomical abnormalities, sexual dysfunction and psychological problems can temporarily or permanently affect male reproductive system leading to infertility. Male reproductive toxins can be encountered in many ways- industrially, environmentally, biochemically, hormonally, genetically, therapeutically, self-administered and life style. The objective of the present review is to summarize results to date of studies examining the adverse effects of various factors on human sperm parameters, morphology of reproductive organs, DNA damage and chromosomal aberrations related to male reproductive system.

Keywords: *infertility, testosterone, oligozoospermia, teratozoospermia, chromosomal aberration, conception.*

INTRODUCTION

On a world wide scale, 50-80 million people suffer from infertility. The World Health Organization (WHO) estimated approximately 8-10% of couples suffers from this problem. However, it varies from region to region. About 3 million men are considered infertile in USA. In Australia, every fifth couple suffers due to infertility (Lyttleton, 2004). In India, 15-20% of people of fertile age suffer from infertility (Delhi-IVF.com), one of the pressing problems of this time. Infertility may be defined as a conditional inability to achieve conception on one year or after one year of unprotected coital exposure (Olayemi, 2010). In context of male, a man is said to be infertile if he is unable to impregnate his partner after one year of unprotected intercourse.

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It is reported that sperm production has been declining over the last 50 years (Carlsen et al, 1993). The morphology of sperm a functional ovum is considered as the ultimate criteria of its function. Sperm cells have two components and four parts. Two components of sperm include genetic component and metabolic component. Cell is one of the most conservative structures of animal kingdom. Male infertility is directly linked to quality and quantity of sperm within the semen. The ability of the sperm to fertilize metabolic component. While genetic component takes part in the fertilization event, metabolic component aids to survival and motility of sperm. Any morphological change is likely to have adverse effect on the functional efficiency of sperm. Empirical evidences indicate that double headed sperms, sperms having defective tail or dysfunctional acrosome or other morphological defects are incapable of taking part in fertilization process. Morphological abnormality of sperm (tetratozoospermia) and insufficient sperm

motility (asthenozoospermia) are some of the aspects of infertility. The major factor responsible for male infertility is either low sperm concentration (oligozoospermia) or total lack of sperm in semen (azoospermia) (Feng, 2003). Among all of these, oligoasthenoteratozoospermia is most frequent (Isidori et al, 2005). The disorders of the function of epididymis *i.e.* during ejaculation and erection of sperm and seminal fluid *via* the penile urethra can disrupt sexual and reproductive health. A number of effective therapies can be used to treat these disorders (Behre, 2008). Impotency is a condition in which male partner fails to deposit sufficient number of sperms within the vagina of his partner as a result of improper male sexual response either due to lacking the steps of erection, emission and ejaculation or penile dysfunction or testicular damage. Erectile dysfunction (inability to achieve or have sustained erection) may be an important factor/contributor in male infertility. It is important to identify the patients with infertility, not only to allow reproductive potential but also to identify a population susceptible future. Recent researchers have indicated that male infertility occurs due to a number of causes and factors. Male factor infertility is a complex disorder that affects a large sector of the population; however, many of its etiologies are unknown. By elucidating the underlying genetic basis of infertile phenotypes, it may be possible to find the reasons responsible for infertility and determine its effective treatments. There are many papers reported on different factors responsible for male infertility (Olayemi, 2010; Feng, 2003; Brugo-Olmedo et al, 2001; Saradha and Mathur, 2006; Hammoud et al, 2008; O'Flynn O'Brien et al, 2010). In this review paper we have tried to enlist some of those factors and their impact on male fertility:

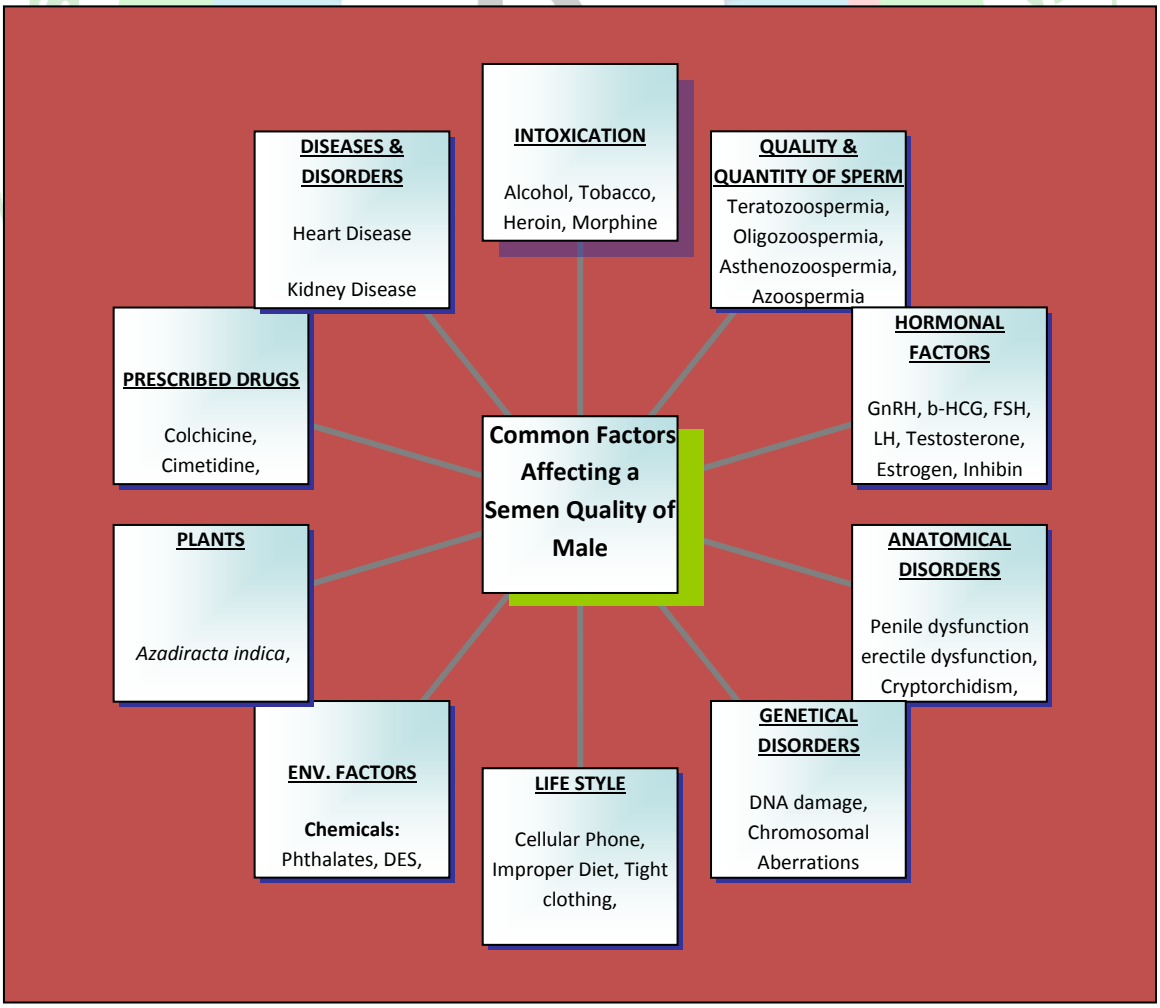

Fig 1. Overview of Common Factors Affecting a Semen

Quality and quantity of sperm within semen

Success of a mating is dependent upon both quality and quantity of semen delivered to the female. While a quality aspect of sperm denotes its morphological design; quantity denotes whether sufficient numbers of sperms are present in semen. Sperm quality can be assessed by its motility, viability, maturity, morphology and sperm tail membrane integrity. Sperm disorders include defects in quality or quantity of sperm produced and defects in sperm ejaculation (Rebar, http://www.merckmanuals.com). The normal volume of semen per ejaculate is approximately 2.5 ml to 5ml having a minimum of 20 million sperms per ml of semen in order to affect a fertilization event and achieve pregnancy (Olayemi, 2010). Anything below this is considered sub optimal and leads to the development of oligozoospermia and even azoospermia that can be due to a variety of factors: defective seminiferous tubules, faulty spermatogenesis, diet (vitamin E deficiency has been shown to enhance the occurrence of infertility in animal models), and life style changes due to forces of industrialization, urbanization and globalization. Two aspects of semen quality are quite important - ability of sperm to reach fertilization site or ability of fertilizing sperm to carry out the fertilization process and early embryo development (Saacke et al, 1994). Mainly genetic and epigenetic factors of both male and female are responsible for successful embryo development; sperm and semen quality has also adverse affects on embryo quality and development, the mechanisms involved are known few (Chenoweth, 2007). The diagnosis of sperm disorders can be done by semen and genetic testing. A semen analysis measures the quantity and quality of both the liquid portion- semen and the microscopic, moving cells- sperm. The male reproductive dysfunction can be diagnosed by modern techniques of endocrine and radiologic evaluations (Patel and Niederberger, 2011). The most effective treatment is usually *in vitro* fertilization *via* intracytoplasmic sperm injection (ICSI).

Hormonal Disruption and Hormonal Imbalance

In vertebrates, hormones play a major and central role in the growth, development, metabolism and reproduction. Hormones reinforce homeostasis by controlling and coordinating various body activities Testicular dysgenesis syndrome (TDS) is a congenital derangement of seminiferous tubular structure and function, inextricably linked to improper concentration of sex hormones at different stages of life cycle leading to male infertility. Development, organization and operation of male reproductive system also as male fertility is regulated and influenced by a number of hormonal factors *viz.* gonadotropin releasing hormone (interstitial cell stimulating hormone-ICSH from hypothalamus, follicle stimulating hormone-FSH, luteinizing hormone-LH), inhibin and activin (from sertoli cells), androgens (testosterone and related sex steroids from testis and adrenal cortex) and estrogens. Hormonal factors work in a mutually interacting circuit wherein they have self-limiting effects on their own rates of manufacture and secretion. Infact, most of the hormones operate by means of a negative feedback mechanism. For instance, if there is shortage of testosterone (either due to endogenous factor or due to exogenous factor) or hormonal pulse is denied (due to defective testis) then male reproductive organs will not develop properly, leading to infertility. The hypothalamus and pituitary gland controls the dual task of testis: production of immature spermatozoa (spermatogenesis) and production of testosterone (steroidogenesis) which in turn controls hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary gonadotropin secretion by negative feedback regulation. In addition, reduction in the optimal concentrations of either GnRH or GnRHF due to injury or metabolic block may also contribute to male infertility. Testosterone deficiency leads to a clinical condition called as hypogonadism. Effective therapy can be achieved by substitution with modern testosterone preparations for treatment of the patients (Behre, 2008). The

abnormalities such as reduced sperm production and fertilizing capability occur in male reproductive system due to irregular action of androgen during development (Hayashi et al, 2001). Recent researchers have indicated that copious quantities of circulating estrogens may suppress the spermatogenesis and adversely affect the male fertility power. Certain dairy products consumed for a long period of time, imbalances the body hormones and enhance the level of estrogen which is detrimental to male fertility. Germ cell tumors produce b–human chorionic gonadotropin (b-HCG) and a-fetoprotein (AFP). The increased level of b-HCG of intratesticular estradiol production decreases/impair the spermatogenesis in the contralateral testis (Hayashi et al, 2001; Morrish et al, 1990) while increased level of AFP decreases total sperm count-oligozoospermia (Hansen et al, 1989). Moreover, the patients suffering from germ cell tumors had an increased level of serum follicle stimulating hormone (FSH), a rare cause of treatable male infertility. Giltay et al, 2004 reported the beneficial effect of FSH treatment on extremely oligoteratozoospermic males. Inhibin B is a better marker of spermatogenesis than FSH or LH for the evaluation of male fertility status (Kumanov et al, 2006). Recent researches have been done on different polymorphisms of the FSH receptor gene for outcome of FSH treatment. Sex hormone binding globulin (SHBG) delivers sex hormones to target tissues. Plasma SHBG levels tended to be lower in idiopathic infertile men (oligoasthenoteratozoospermia-OAT) compared to normal fertile men; affecting sperm count, sperm motility and sperm morphology. However, much attention is required to elucidate the role of SHBG gene polymorphism in male infertility. Recent population-based studies suggest endocrine dysregulation in obese men as they exhibit reduced inhibin B levels and elevated estrogen levels which reduce androgen and SHBG levels, explaining the increased risk of abnormal semen parameters and infertility(Hammoud et al, 2008). No therapeutic measures for obesity-associated male infertility have been studied yet. Thus, greater clinical awareness is needed for understanding its mechanism and treatment. AMH (anti-mullerian hormone) is positively correlated with sperm concentration and semen volume & inhibin B with sperm concentration and motility, while DNA damage and TAC is negatively associated with sperm motility and sperm concentration, respectively. There is no significant relationship between hormone concentration, sperm DNA damage and total antioxidant capacity (TAC) that suggests other mechanisms for sperm dysfunction (Appasamy et al, 2007). Moreover, the use of androgens should be prohibited as they may retard spermatogenesis (Kumar et al, 2006). More recently, andrologists use the modern assisted reproduction techniques (ARTs) *i*.e. intracytoplasmic sperm injection (ICSI) to improve the fertility of the single sperm cell to obtain better results (Isidori et al, 2005).

Anatomical Abnormalities

Various disorders in different organs of the male reproductive system might cause testicular or post-testicular abolition of fertility (Behre, 2008). In industrialised countries, one of the major anatomical abnormalities related with male infertility is a condition known as cryptorchidism, affecting 2-4% of male infants, more frequent in premature infants (Hutson et al, 2010). In this condition, testicles fail to descend into scrotal sacs before birth. Abdominal testicles are unable to support the process of spermatogenesis because it requires temperature (2ºC) below the normal human body temperature for sperms cells to mature into viable, functional and fertilizable sperms. However, the exact cause of cryptorchidism remains elusive. Various factors, mainly hormonal, genetic and environmental factors may contribute to the development and increased incidence of cryptorchidism. This increases the risk factor for impaired infertility (33% to 66%) and testicular cancer, 5-10 times greater than normal (Robin et al, 2010). Jensen et al, 2010 presented a report in support of intrauterine environment and maternal inheritance contributing to the phenomenon of cryptorchidism. According to another

research, the spontaneous testicular descent is infrequent in infants with cryptorchidism and is rare in infants below the age of 6 months (Wenzler et al, 2004). Although, the long-term therapy is still in its infancy, the surgical treatment by orchiopexy is recommended between 6 and 12 months as to preserve the spermatogonia (Hutson et al, 2010). Early surgical therapy may reduce the risk of subfertility and/or malignancy. The patients who undergo orchiopexy after the age of 12 years or no orchiopexy have 2 to 6 folds of risk of testicular cancer as compared to those who undergo between 10 to 12 years of age (Wood and Ejder, 2009). Although, hypospadias is not closely associated with cryptorchidism due to major difference in pathogenesis; placental abnormality may cause both cryptorchidism and hypospadias as it occurred in many other congenital malformations (Thorup et al, 2010). Chromosomal abnormalities in patients with cryptorchidism and hypospadias have been reported (Moreno-Garcia and Miranda, 2002). In addition to cryptorchidism, varicocoels and tubular damage / dysfunction due to infection may contribute to male infertility.

Chemical / Occupational / Environmental exposure

In modern world, economy is based on the notions of conspicuous consumerism, mass-scale methods of production, ever expanding industrial processes and rising trends of chemical farming have exposed man to umpteen numbers of chemicals which were not even in thought for decades ago. An estimated one lakh chemical are produced every year for various uses. Pesticides have been in use since the early days of modern agriculture but rising use of chemical fertilizers and pesticides in agricultural practices exposes human beings to a plethora of chemicals which are not only detrimental to general health but also poses serious threat to reproductive ability. Many chemicals that are produced at industrial scale are carcinogenic and cause testicular cancer. Cancer of testicles is one of the factor which leads to the development of male infertility. The incidence of infertility and abnormal semen parameters occurs in men and experimental animals exposed to agricultural chemicals is similar to that of occupational exposure of chemical agents (Gerber et al, 1988). Sulfasalazine (SASP) might cause male infertility by inducing oxidative stress (Alonso et al, 2009). The chemicals which are capable of crossing placental barrier transmit from mother to foetus. Many chemicals accumulate in the amniotic fluid and interfere with normal gonadal development of foetus. Testicular dysgenesis syndrome (TDS) is a condition in which there is damage to testicles by multiple mechanisms including chemical exposure. Many endocrine disrupting chemicals have been shown to cause TDS linked disorders in animal exposure studies, such as diethylstilbestrol, Bisphenol A, flutamide, vinclozolin, diethylpathalate (DBP) and diethylexylpathalate (DEHP). Several people as part of their job/ occupational/ professional are exposed to a number of chemicals including heavy metals which cause a number of deformities and abnormalities in human body including male infertility. There are many chemicals that can temporarily or permanently affect the fertility of men either by altering spermatogenesis, sperm parameters or hormonal imbalance. Among such chemicals are lead (Braunstein et al, 1978; Cullen et al, 1984), diaminostilbene (Landrigan et al, 1983), chloroprene (Sanotsky and Fomenko, 1986), benzo(a)pyrene (BaP) (Inyang et al, 2003), dibromochloropropane (Whorton et al, 1977), carbon disulfide (Meyei, 1981; Wagar et al, 1981), alkyl mercury (Henderson et al, 1986), ethylene glycol ether (Welch et al, 1988), methylene chloride (Kelly, 1988), manganese (Lauwerys et al, 1885), Carbyl (Wyrobek et al, 1981) and vinyl chloride (Makarov, 1984). Prenatal diethylstilbestrol (DES) exposure may slightly increase the risk of infertility, but does not affect the number of fathered pregnancies or live births (Perez et al, 2005). Among heavy metals; lead was first to be reported to have antifertility effect. Moderate exposure to lead and cadmium can decrease semen quality (Telisman et al, 2000).

Exposure to copper can result into oligoteratozoospermia and asthenozoospermia (Lahdetie, 1995). In human studies, Mortensen et al, 1988 observed reduced sperm quality in welders exposed to chromium. The nematocide dibromodichloropropane (DBCP) have negative effect on spermatogenesis (Rees, 1993). Ethane 1,2-dimetane sulphonate (EDS) cause toxicity to Leydig cells as a result of lack of plasma testosterone level (Sprando et al, 1990). Boric acid is also a reproductive toxicant which reduces the testosterone (Fail et al, 1995). Chromium compounds mainly cause testicular tissue damage by increasing oxidative stress (Acharya et al, 2004; Hall, 1994). Aluminium causes reduced weight of reproductive organs and impair fertility (Guo et al, 2005). Ammonium metavanadate is reported to have toxic effect on reproduction and fertility (Morgan and El-Tawil, 2003). Certain pesticides are able to disturb the sex steroid hormone system and act as antiandrogens. Exposure to pesticides may cause foetal loss, alteration in gestational age at delivery, formation of terata (birth defects), infant/child morbidity and mortality, male/female sexual dysfunction, sperm abnormalities, amenorrhea, dysmenorrhea and illness during pregnancy and parturition and endocrine effects. Male infertility could be associated with exposure of mothers of subfertile men to environmental organochlorine, dichlorodiphenyldichloroethylene (p,p′-DDE), restricted to intra-uterine and thus undetected in subfertile men (Charlier and Foidart, 2005). A research paper explored that higher concentration of chlorinated pesticides viz. α-, β-, γ-, δ-HCH, DDT, pp′DDE and pp′DDD affect semen quality parameters, causing infertility (Pant et al, 2007). Pesticides affect the particular stages of reproduction, mainly the prenatal stage and results in damage to the reproductive organs and ultimately impair fertility (Iyer, 2010; Iyer P and Makris, 2010). Prenatal exposure of phthalates in the womb of human adversely affects male reproductive system and impairs testicular functions (Swan et al, 2005). Many pesticides particularly persistent organic pollutants (POP) i.e. non-metabolic and non-biodegradable are serious reproductive toxicants, which upon entering into food chain get biologically magnified and cause serious problems into human system including reproductive toxicity and infertility. 1,2-dibromo-3-chloropropane (DBCP) causes dose dependent reduced fertility by effecting post-testicular sperm through the mechanism of decrease in the metabolism of glucose to CO2 by epididymal ejaculated sperm (Kluwe et al, 1983). Human sperm chromatin condensation can be altered by exposure to organophosphorus (OP) with greater susceptibility to DNA denaturation and may adversely affect reproductive system via a mechanism of protein phosphorylation (Sanchez-Pena et al, 2004). Although the basic mechanism of antiandrogenic pesticides to irregulate the sex steroid hormone system is not clear, it may act as 5α-reductase inhibitor which can interfere with endocrine system (Lo et al, 2007). In recent technique, advanced treatments in sperm-to-ovum injection and sperm retrieval, successfully make possible for the infertile men to reproduce their own progeny (Wald, 2005). Epidemologic studies found the association of occupational exposure to pesticides with an increased risk of delay of conception and an increased risk of spontaneous abortion among wives of exposed workers (Petrelli and Mantovani, 2002).

Genetic / Congenital Factors

There is a general consensus amongst the scientific fraternity that genes are important and primary. In genetic aspects, sperm DNA integrity is crucial for the accurate flow of genetic information in the offsprings. Each and every gene has been characterized for specific roles, the accurate transmission of epigenetic information influence fertility in males and in their offsprings. They determine the conditions of individual from womb. Genetic pre-disposition is certainly an important aspect in the development and progression of most of the diseases and accounts 10-15% for severe male infertility including chromosomal aberrations and single gene mutations. Variability in the differential gene expression and its

modification constitute an important component of epigenetic which has critical role in sperm development and function, fertilization and post fertilization events. Defective spermatogenesis lead to male infertility either due to pituitary disorders, testicular cancer, germ cell aplasia, varicocele, environmental factors or defective sperm transport by reason of congenital abnormalities or immunological and neurogenic factors. Interference with germ cell generation and maturation or production of non-functional spermatozoa increases the frequency of genetic disorders associated with male fertility (Iammarrone et al, 2003). The gene CREM and ACT have regulatory functions in human spermatogenesis and help to understand its molecular mechanisms (Krausz and Corsi, 2005). Defective sperm function (due to poor semen quality and a high incidence of nuclear and mitochondrial DNA damage) and childhood diseases including dominant genetic mutations (such as achondroplasia and cancer) are also thought to play a major role in the aetiology of human infertility. The factors such as paternal age and environmental toxicants responsible for poor semen quality initiate DNA strand breakage in the spermatozoa, causing mutation in the embryo (Aitken et al, 2003). DNA repair system is inevitable for maintaining genetic stability and normal spermatogenesis. The nucleotide-excision repair (NER) system is necessary for the deletion of bulky DNA adducts during spermatogenesis. The XPA (–4) G/A polymorphism in XPA promoter of NER pathway lowers the transcriptional activity and increases sperm DNA damage and thus may contribute to male infertility (Gu et al, 2010). Currently, there are four methods to measure sperm DNA fragmentation *i.e.* Comet assay, Tunel assay, Sperm Chromatin Structure Assay (SCSA) and the Acridine Orange Test (AOT) (Evenson and Wixon, 2006). Infertile male affected by some forms of genetic alterations produces a high frequency of sperms with aneuploidies as a result of constitutional genetic abnormality or meiotic errors induced by the altered testicular environment (Ferlin et al, 2006). Although genetic factors express differently in different environment conditions, yet to some degree of genes determine the nature of disease states. The polymorphic gene CYP1A1 (CYP1A1*2A CC genotype) encodes CYP1A1 enzyme that catalyzes the bioactivation of polycyclic aromatic hydrocarbons (PAHs) which are able to form DNA adducts. The DNA adducts in sperm cells can cause severe DNA damage and interfere with meiotic division during spermatogenesis, which can be related with infertility in men (Vani et al, 2009). It has been recently reported by Aydos et. al. (2009) that the genetic polymorphisms of glutathione S-transferase (GST M1 and GST T1) and CYP1A1*2C of xenobiotic-metabolizing enzymes may possibly play an important role in male factor infertility (Aydos et al, 2009). Safarinejad et al in 2011 has investigated the association of the (TAAAA)*n* repeat and Asp237Asn polymorphisms in the sex hormone- binding globulin (SHBG) gene with idiopathic male infertility and relation to serum SHBG concentration. It has been demonstrated that Asp237Asn polymorphism and long SHBG (TAAAA)*n* alleles (*i.e.* >8 repeats) in SHBG gene may affect SHBG levels and thus increases the risk of infertility. Studies has also been carried out to investigate whether the polymorphism in aryl hydrocarbon receptor (AHR), aryl hydrocarbon receptor repressor (AHRR) and aryl hydrocarbon receptor nuclear translocator (ARNT) genes of aryl hydrocarbon receptor pathway are associated with male factor infertility in Estonian men. Allele and genotype frequencies were compared between infertile men and controls and separately in the normozoospermia, oligozoospermia and azoospermia groups. It was found that AHRR (Pro185Ala) polymorphism contribute to male infertility development (Merisalu et al, 2007). Some genetic problems with chromosomes occur in about 2 to 20% of infertile men and can affect their fertility in two ways (a) Male sex partner having chromosomal abnormalities can disrupt cell division and sperm production (b) The development of testicles may be affected by chromosomal disorders mainly of sex chromosome, of which Klinefelter's

syndrome is the most common with an additional X chromosome (47 XXY). In chromosomally derived infertility, spermatogenic breakdown results due to Y chromosome microdeletion (with a frequency of 9.1%) and structural chromosomal abnormalities, which are linked with histological changes in testis (Vicdan et al, 2004). Double minute chromosome is positively related to double-stranded breaks, poor semen parameters and regulation of DNA repair (Papachristou et al, 2008). However, in the case of genetic infertility, the molecular mechanisms of spermatogenic damage (for example Yq microdeletions) are still not known. It can be known only by large scale association studies and testicular or spermatozoal expression studies in altered spermatogenesis (Ferlin et al, 2007). The interstitial Y-chromosomal microdeletions of SRY gene (associated with gonadal differentiation) and DAZ, SPGY and related genes on the Y chromosome (associated with spermatogenesis) encompassing the AZF a, b or c region cause genetic abnormalities and eventually male infertility (Thielemans et al, 1998). Mutations in the genes required for fertility cause infertility due to defects in development of the germ cell lineage. The DNA can be repaired *via* increased frequency of mutations in DNA with meiotic arrest in infertile male (Fox and Pera, 2002). Novel technologies may help in further understanding the etiology of male factor infertility through the identification of specific infertile phenotype signatures (O'Flynn O'Brien and Agarwal 2010). As already discussed in hormonal section that excessive exposure to estrogen negatively impacts spermatogenesis, the polymorphisms of the estrogen receptor (ER) genes have been implicated in male infertility. ER-α (ESR-1) PvuII TT, ER-α XbaI AA, ER-β (ESR-2) RsaI AG, and ER-β AluI AG genotypes are associated with increased infertility risk, significantly lowers the level of serum sex hormone binding globulin (SHBG), luteinizing hormone (LH) and values for sperm density, sperm motility, and percentage of sperm with normal morphology (Safarinejad et al, 2010). However, further researches are needed to establish better association between the biological mechanism of ESR-α, and ER-β and incidence of male infertility.

Receptor Dysfunction and defect in biosignalling pathways

In several cases development and organisation of male gonadal organs are affected by faulty receptors mediating the biosignalling pathway of sex steroids. As discussed in the previous section the development of male sex organs requires an optimal interplay between various hormonal factors particularly testosterone. Male sex hormone *i.e.* testosterone works in a paracrine manner and its effect in the target cell is mediated by cytosolic receptor (TFM). A defective receptor is not able to mediate the function of testosterone and these results into the development of the clinical conditions known as testicular feminization or androgen insensitivity. Androgen insensitivity may be considered as a factor of male infertility.

Alcohol Intoxication and Smoking

Empirical evidences and few studies have suggested that regular consumption of alcohol negatively impacts the fertility power in men. Alcohol not only reduces the sperm counts and concentration but may also induce morphological deformities in sperm (*e*.g. double headed sperm) which makes sperm incapable of fertilization. There are evidences to indicate that miscarriage is also associated with alcohol. A research paper reported that heavy chronic alcohol intoxication have a slow progressive negative impact-moderate teratozoospermia followed by oligoasthenoteratospermia, then a severe cryptozoospermia and ultimately azoospermia. At this stage the maturation of germinal cells at the pachytene stage was arrested and no mature sperm cells were found. However, alcohol withdrawal allowed fast and drastic improvement of the semen parameters to normal within 3 months (Sermondade et al, 2010). Sperm concentration, percentage motility, morphology, and percentage viability are significantly affected due to tobacco chewing

in Indian men that lead to infertility (Said et al, 2005). Cigarette smoking and passive inhalation of smoke may adversely impact male fertility. Smoking on a regular basis has been shown to reduce sperm count in males. Most of the reports showed negative impact of cigarette smoking on male reproductive system; such as lower semen volume, reduced sperm count, production, motility, viability, morphology, fertilising capacity of spermatozoa through increased seminal oxidative stress, DNA damage and lower implantation rates of embryos, correlated with cigarette smoking/day and smoking duration(Soares et al, 2007; Ramlau et al, 2008; Mostafa, 2010). In addition to above, there is increased seminal leucocytes, oval sperm percentage, defective head-piece spermatozoa and spermatozoa with cytoplasmic droplets in smokers (Mak et al, 2000; Trummer et al, 2002; Hassa et al, 2006; Bouvet et al, 2007; Ramlau et al, 2007). Moreover, it decreases the antioxidant activity of superoxide dismutase and increases leucocytospermia which adversely affect sperm motility (Pasqualotto et al, 2008) but the negative impact of smoking on intracellular antioxidant enzymes does not increase oxidative DNA damage (Viloria et al, 2010). Nicotine, the main constituent of smoke has a significant impact on sperm morphology and sperm count (Gornig and Schirren, 1996). Consumption of >20 cigarettes/day shows elevated seminal Cadmium (Cd) level in smokers (Chia et al, 1994). Smoking has negative correlation between cadmium in blood and sperm density (Saaranen et al, 1989). Also, lead in seminal plasma affects fertility of men (Kiziler et al, 2007). Beside above, smoking also induces erectile dysfunction associated with vascular (arterial and venous) impotence, elevated serum estradiol levels and lowered sperm density, greater numbers of leucocytes in the seminal fluid and lower sperm penetration with greater associations in patients with pre-existing impaired function (Wolf and Shulmam, 1996). On analysing the degree of DNA fragmentation in spermatozoa using the TUNEL-assay with flow cytometry detection, it is found to be higher in smokers concluding that smoking may have negative impact on sperm nuclear quality (Sepaniak et al, 2006). Including the research papers indicating nonsignificant association of semen parameters with smokers and non-smokers, it is concluded that men with marginal semen quality experience reduced fertility which regarded smoking as an infertility risk factor (Vine et al, 1996; Practice committee of American society for reproductive, medicine, 2008). Even male cigarette smoking can significantly decrease live birth rates (Fuetes et al, 2010). However, further studies are required to establish this beyond reasonable doubts.

Desk bound work/Tight clothing/Mobile phones/Diets

In recent years a number of lifestyle factors have been suggested which may be adversely affecting the male fertility. Unhealthy and imbalanced lifestyle increases the occurrence of impotence. Desk bound work, tight clothing, composition of diet and keeping mobile phones close to scrotum may all have some effect on male fertility. However it is still unclear as to how these factors are actually exerting their effects. Further studies are required to establish a concrete link between lifestyle factors and incidence of male infertility. Vitamin E supplement increases the semen quality and quantity parameters by protecting testicular cell membrane and mitochondria from antioxidant activities (Yue et al, 2010). Deficiency of it increases the risk of male infertility. Isoflavone and phytoestrogens in soyabean cause adverse effect on the development and function of the male reproductive system. Wdowiak et al, 2007 studied the effect of GSM equipment on the semen and found an increased proportion of abnormal sperm cell morphology positively related with the time period of exposure to the waves emitted by the GSM phones and decrease in sperm cells progressing motility in the semen with the frequency of using mobile phones. People using mobile phones to a greater degree may be exposed to stress, which by affecting the level of cortisol, prolactin and testosterone may contribute to the decrease in concentration of the semen (Sheiner et al, 2003). Human studies have

shown direct relationship between obesity and infertility. Ghanayem et al, 2010 demonstrated that diet induced obesity in male mice cause a significant reduction in male fertility. Obesity resulted in reduced number of plugs and pregnancies of control females paired with obese versus lean males.

Disease and fertility in man

Mumps, tuberculosis and sexually transmitted diseases can affect sperm production by causing inflammation and obstruction in the male genital tract. Cryptorchidism occurs in 2-5% of male babies in western countries (Paulozzi, 1999). Males born with this defect are also at a higher risk from testicular and breast cancer in later life. There are several general medical disorders or conditions that may reduce male fertility-

Fever-

There is a possibility that a prolonged fever could affect sperm production. In cases of pneumonia, influenza or even severe cold results in high fever inhibits production of sperm and its quality. These changes usually recover over a few weeks. Mediterranean fever causes azoospermia in Turkish men without colchicines treatment by mutation in gene M680I, M694V, M694I, V726A, P369S, and A744S (Etem et al, 2010).

Microbial Infection-

The infectious agents such as bacteria, fungi, viruses and parasites may interfere human physiological functions including reproduction in both the sexes. About 15% cases of male infertility are due to the infection of male genito-urinary tract. It can affect different sites of the male reproductive tract, such as testis, epididymis and male accessory sex glands and spermatozoa at different levels of their development, maturation and transport resulting from testicular damage, autoimmune processes induced by inflammation and secretory dysfunction of the male accessory sex glands. *Chlamydia trachomatis* and *Nisseria gonorrhoeae* are the most common microorganisms affecting male fertility. Though there are several reports, the data on the influence of urogenital tract infections of fertility are paradoxical.

Diabetes-

Surplus sugar in blood can directly affect the quality of sperms and gradually lead to male infertility. In the cases of chronic diabetes, functions of Autonomic Nervous System are damaged which results in problems associated with erection and ejaculation. It has a direct effect on fertility causing DNA damage in sperm (Mallidis, 2008). Impotence is extremely common among diabetics which affect the nerves to the penis. It can never restore erectile function as the basic diabetic process can never be reversed.

Stress-

It causes many changes in the body at hormonal level affecting fertility. Difficulty with erection either directly or indirectly is a major problem associated with hypertension. Stress reduces a man's libido. Under much stress condition they often lack of sexual desire. This happens due to increase blood pressure and irregular blood circulation throughout the body, decreasing the amount of blood going to the penis.

High blood Pressure-

High blood pressure is another condition that affects impotence, and which is often a result of poor lifestyle choices. This may be because of increased blood pressure which may damage small vessels in the penis or that hormonal levels are affected. Added weight, lack of exercise, an unhealthy or high-sodium diet, and alcohol, all contribute to high blood pressure.

Coronary artery disease-

Coronary artery diseases impact adverse effect on fertility by causing erection problems either due to hardening of the arteries in the penis and heart or due to drugs used in the treatment of heart defects and diseases.

Neurological disorders-

Diseases like multiple sclerosis, stroke, and spinal cord injury can interfere with erection and ejaculation.

Kidney diseases-

Sperm quality and fertility is negatively affected by chronic renal failure and can also cause erection problems.

Cancer-

Fertility can be greatly reduced by those types of cancers that mainly affect endocrine system and genital tract. The chemotherapeutic measures such as drugs and radiation used for the treatment of cancer severely reduce sperm production (oligozoospermia) and even lead to azoospermia.

Emotional Contributors-

As the brain controls all the functions of our body; its functions can also affect sexual excitement and performance. Depression affects cognitive and emotional functioning and often colours and confuses mental stimuli. Some antidepressants also negatively affect sexual desire and performance.

Drugs

Studies have shown that many medicinal plants and drugs, used in the treatment of various diseases are detrimental to reproductive health as they can induce infertility. Some types of prescribed medicines that can lead to male infertility are high blood pressure monitoring drugs, antibiotics, CNS depressant and drugs used for treatment of gastric problems that interfere with sperm production and ejaculation. Some of the common drugs that can cause fertility problems are enlisted below:-

Calcium channel blockers:

Calcium channel blockers are typically prescribed for patients of hypertension. They increase amount of blood and oxygen supply to heart helping to minimize the work of the heart. However, they interfere with the fertilization process as prevent the sperm from being able to penetrate an egg.

Cimetidine:

Cimetidine used as an ulcer medication, helps to reduce the amount of acid produced in the stomach. Regular use of the drug can results in infertility. In men, it decreases the levels of LH and testosterone resulting into reduced sperm count.

Antibiotics:

Antibiotics are often prescribed to deal with a variety of bacterial infections and problems. Some antibiotics show short term and others have long term effects. Some antibiotics that are known or suspected to interfere with male fertility include: Nitrofurantoin is used in Urinary tract infections its reduced sperm count. Neomycin, Macrolides, Ketoconazole medically used for Bacterial and fungal infections it's also reduced sperm production and motility

Chemotherapy:

Fertility is affected when patients of cancer undergo chemotherapy as well as radiation therapy. Often, the drugs used in chemotherapy result in severe decrease in sperm count and motility. These effects can be temporary or permanent.

Conclusion

A wide range of factors and causes contribute to the development and progression of male infertility. Overall, fertility issues are usually caused with the state of one's general health. Men who live a healthy lifestyle are more likely to produce healthy sperm. Although many treatment options are available, many times treatments do not work. Thus there is a need to limit the exposure of human beings to noxious chemical agents, pesticides, fertilizers, drugs, radiations, stressful lifestyles etc. which may be contributing to male infertility. Governments all over the world ought to come up with the progressive legislation which can phase out the manufacture, use and disposal of hazardous chemicals. In this context REACH

(Registration Evaluation and Authorisation of chemicals), a legislation floated by EU is a welcome gesture. Finally a sound and informed public opinion must be created so as tackle the issue of male infertility.

Table 1: Summary of factors emphasizing male infertility

Sr.	Exposed Factor	Reproductive Outcomes	References
	PESTICIDES		
1	Ops & Is	Reduced sperm concentration.	(Paduntod et al, 2000)
2	Hs, Is, Fs	Reduced sperm concentration & sperm motility.	(Oliva et al, 2001)
3	PCBs & p,p'-DDE	Abnormal sperm morphology & reduced sperm concentration. Only PCBs reduce sperm motility.	(Hauser et al,)
4	Abamectin	Significantly reduced fertility, sperm counts, daily sperm production and serum level of testosterone.	[129]
5	CB-153	Reduced sperm motility and free testosterone levels in young men.	[130]
6	DDT	Reduced sperm concentration.	[131]
7	HCB & DDT	Infertility.	[132]
8	Carbyl, CPs	1-Napthol: reduced sperm concentration & sperm motility.	[133]
9	PCBs & p,p'-DDE	Higher serum concentrations of CB-153 and p,p'-DDE in infertile males.	[134]
10	Ops	Reduced semen volume & poor motility.	[135]
11	Organohalogens	Positive associations between CB-153, p,p -DDE and SHBG. Gonadotropin levels and SHBG seems to be affected by POP exposure.	[136]
12	Fenvalerate	Reduced sperm concentration.	[137]
13	PCBs	Reduced sperm motility.	[138]
	CHEMICALS		
14	Manganese chloride solution	Reduced fertility.	[139]
15	Macrocyclic complexes of manganese(II)	Reduced weight of the testes, epididymis and seminal vesicle. Reduced sperm motility and Sperm density in testes. Decreased biochemical activity.	[140]
16	Ammonium metavanadate	Reduced fertility.	[57]
17	Chromium (Cr) (VI) compounds (CrO_3)	Reduced sperm count level.	[54]
18	Methanol	Adverse effects on reproductive system.	[141]

19	Phthalates	Testicular toxicity and reduced fertility	[62]
20	Prenatal DES	Reduced fertility	[47]
21	DDT and p,p'-DDE	Reduced sperm motility, poor semen parameters morphological tail defects, Insufficient sperm chromatin condensation, of incomplete DNA condensation.	[142]
22	Lead	Increase in immature sperm concentration, infertility and increased risk of spontaneous abortion in wives of exposed men.	[143]
24	Phthalates metabolites	Monoethyl phthalate (MEP) reduce sperm concentration and low morphology. Adversely affect human semen quality.	[144]
	PLANTS		
25	*Piper betle* (leaf-stalk)	Suppress cauda epididymal sperm count and motility.	[145]
26	*Acyranthus aspera*	Antiandrogenic effect. Reduced epididymis weight, sperm motility, sperm count, testosterone level and biochemical changes in testicular elements.	[146]
27	*Colebrookia oppositifolia* (leaf extract)	Reduced testes and epididymis weight, sperm count and motility and biochemical activity. Depression of spermatogenesis. 100% infertility.	[147]
28	*Cumium cymium*	Antispermatogenic effect. Abnormal cauda, epididymal spermatozoa. Reduced seminiferous tubule diameter and sex organ weight.	[148]
29	*Solanum xanthocarpum*	Inhibit spermatogenesis. Reduced testosterone level, impair LH action on Leydig cells and decreased no. of surface bound LH receptor.	[149]
30	*Aegle marmelos* (leaves)	Decreased accessory sex organ weight. Abnormal sperm morphology. Reduced sperm motility, sperm concentration, testosterone & estradiol level.	[150]
31	*Juniperus phoenica L*	Arrest spermatogenesis. Dose-dependent decrease in sperm count and motility. Significant decrease in seminal vesicles and testicular weight and testosterone level.	[151]
32	*Allamanda cathartica L.*	Reversible suppression of fertility. Adverse affects on motility, viability, morphology and on number of spermatozoa in the cauda epididymis.	[152]
33	*Bacopa monnieri*	Suppressed fertility. Reduced sperm motility, viability, morphology, and number of spermatozoa in cauda epididymis. Alterations in the seminiferous tubules.	[153]
34	*Curcuma longa* (rhizome)	Reversible suppression of spermatogenesis and fertility. Reduced sperm motility, viability, morphology, and number of spermatozoa in cauda epididymisand serum level of testosterone.	[154]
35	*Piper nigrum L.* (fruit)	Antispermatogenic and antifertility effects.	[155]

		Adverse effects on sperm parameters, levels of sialic acid and fructose.	
36	*Gossypium sp.*	Antifertility effects.	[156]
37	*Terminalia chebula*	Severe reduction in fertility. Significant decrease in sperm count, motility, and increase in morphological abnormalities of epididymal spermatozoa. Interfere sperm maturation in epididymis.	[157]
38	*Centella asiatica L.*	Antispermatogenic and antifertility effects. Reduced serum sperm count, motility and testosterone level.	[158]
39	*Cassia fistula* (seeds)	Suppresses fertility; organ weights, fertility, circulatory level of hormones and tissue biochemistry.	[159]
	DRUGS		
40	Quinine	Alter morphology of testes and suppress spermatogenesis.	[160]
41	Phenothiazines (Chlorpromazine & Thioridazine	Reduced testicular functions.	[161]
42	Artemether	Reduced sperm count, motility, viability and serum testosterone level.	[162]
43	Ampicillin & Cloxacillin	Reduced weights of testes, epididymis, seminal vesicle and prostate glands and reduced sperm count, motility, viability abnormal spermatozoa.	[163]
44	Colchicine	Reduced sperm production and impaired fertility.	[164]
45	Ketoconazole	Reduced weights of testes and epididymis, serum testosterone level and sperm indices.	[165]
46	Sulfasalazine (SASP)	Induced oxidative stress in testis and epididymis, a possible mechanism of male-induced infertility.	[32]
47	Cimetidine	Adversely affect spermatogenesis mediated through hormone.	[166]

Abbreviations: Ops=Organophosphates; Is=Insecticides; Hs=Herbicides; Fs= Fungicides; PCB=Polychlorinated biphenyl; p,p'-DDE=1,1-dichloro-2,2-bis (p-chlorophenyl ethylene); CB-153=2,2',4,4',5,5'-hexachlorobiphenyl; DDT=1,1,1-trichloro-2,2-bis (p-chlorophenyl) ethylene; HCB=hexachlorobenzene; CP=Chlorpyrifos; POP=Persistent organohalogen pollutants.

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