IJPSR (2014), Vol. 5, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 January, 2014; received in revised form, 17 April, 2014; accepted, 25 April, 2014; published 01 June, 2014

MALE INFERTILITY: CAUSES AND CONTRIBUTORS

Poonam Singh*[1], Rakhi Gupta [1], Devendra Patidar [2] and Rama Kant Singh [1]

Division of Toxicology, Central Drug Research Institute [1], B.S. 10/1 Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, Uttar Pradesh, India
Manipal College of Pharmaceutical Sciences [2], Manipal, Karnataka, India

Keywords:

Infertility, Sperm, Testosterone, Ejaculation, Occupational, Obesity, Lifestyle, Smoking, ROS

Correspondence to Author:

Poonam Singh

Division of Toxicology, Central Drug Research Institute, B.S. 10/1 Sector 10, Jankipuram, Extension Sitapur Road, Lucknow, Uttar Pradesh, India
CSIR-CDRI communication number 8698
E-mail: poonam_singh@cdri.res.in

ABSTRACT: Male infertility is a reproductive health disorder, emerging globally as serious medicaland social problem that results in much trauma, emotional instability and psychological stress of the affected couples. In 50% of the diagnosed cases of infertility males are reported to be the predominant causative factor. Male infertility can assess by the quality and quantity of sperm cells as well as structure. The present review provides an overview on a wide range of factors that are accountable for male infertility. Hormonal imbalances, genetical defects, reproductive anatomical & morphological abnormalities, chemicals & toxins exposure, reactive oxygen species and smoking are the main causative factors. Besides these, pollution, changed lifestyle, lack of proper diet & nutrition, addictions, diseases, medications, illness and psychological problems may also contribute to infertility problems which can temporarily or permanently affect male reproductive system. Some of these factors are lifestyle borne and can possibly be corrected and some are medical which need to be given special attention while some fail to be diagnosed. The knowledge of male infertility is increasing rapidly and will enormously help diagnostic and therapeutic approaches to recuperate human infertility.

INTRODUCTION: Infertility may be defined as a biological inability to achieve conception on one year or after one year of unprotected coital exposure[1]. 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. Male infertility can occur either as an isolated disorder or in combination with other complex disorder or syndrome.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(6).2095-12

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(6).2095-12

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 [2]. Several studies have reported that the semen quality and thus male fertility is declining over past decades in several countries all over the world [3, 4, 5, 6]. However, different geographical areas vary in sperm count and semen quality [7, 8].

Studies from disparate countries also confirmed these differences. The men from western countries-Denmark, Germany and Norway have poor semen quality with a higher risk of testicular cancer in comparison to eastern countries' men-Swedish, Finish and Estonian [9, 10]. Fertility decline has been also reported in eastern European countries-Bulgaria, the Czech Republic, Hungary, Poland,

and Russia [11, 12] as well as in Africa [13]. A decline in fertility, with a reduction in sperm counts is also reported from our country India [14]. A recent report on the status of infertility in India states that almost 50% of infertility is related to reproductive anomalies or disorders in the male [15]. This reduction in fertility from past few decades suggests altered lifestyle, pollution, chemical based foods, lack of nutrition, stress, deskbound work attributes to some extent of infertility. The most commonly attributed factor is increasing industrialization and civilization that exposes hazardous chemicals, pesticides and electro-magnetic waves in the environment that also affect other factors contributing to reproductive disorders. Many cases of idiopathic infertility have a genetic basis such as chromosomal aberration, microdeletion and mutation.

ROS (reactive oxygen species) production and thus apoptosis of spermatozoa frequently occurs in infertility cases as a result of effect of different causative factors, for example, cocaine intake and smoking results into mitochondrial apoptosis and eventually cause sperm DNA damage in a number of ways. All the causative factors results into reduced viability, motility, morphology, and concentration of spermatozoa and different types of derangements in reproductive organs that directly or indirectly cause sexual dysfunction and eventually sterility. Many of these biological factors can be diagnosed and may be solved through medical intervention while some of the cases fail to be traced and termed as unexplained infertility.

Gonadotropins, antioestrogens, carnitines and trace elements may be helpful in improving sperm quality [16]. 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. Erectile dysfunction (inability to achieve sustained erection) may be an important factor/contributor in male infertility. 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 that are responsible for male infertility [17, 18, 19, 20].

Therefore, several major and minor causative factors and their impact on male fertility have been summarized in this review.

Quality and Quantity of Semen: The morphology of sperm cell is one of the most conservative structures of animal kingdom. The ability of the sperm to fertilize a functional ovum is considered as the ultimate criteria of its function. Male infertility is directly linked to quality and quantity of sperm within the semen. Success of a mating depends upon both quality and quantity of semen delivered to the female and ability of sperm to reach fertilization site or ability of fertilizing sperm to carry out the fertilization process [21]. Sperm disorders include abnormalities in quality or quantity of sperm produced and sperm ejaculation. More than 90% of cases of male infertility are because of low sperm counts and/or poor semen quality [22].

Sperm abnormalities can be caused by numerous factors, ranging from congenital birth defects and genetic disorders to lifestyle habits and environmental exposures. In many cases, the reasons for sperm abnormalities are unknown. Sperm quality can be assessed by its motility, viability, maturity, morphology and sperm tail membrane integrity. The normal volume of semen per ejaculate is approximately 2.5ml to 5ml having a minimum of 20 million sperms per ml of semen in order to affect a fertilization event and achieve pregnancy [19].

Though, sperm concentration fluctuates, they can be temporary or permanent, depending upon the causal factor. However, recently, sperm criteria have been reassessed and lower reference points for semen and sperm characteristics have been established by direct, retrospective selection of fertile men, defined as men whose partner conceived within 12 months after stopping use of contraception.

The reference values for human semen from fertile men were determined approximately 1.5ml normal volume of semen having 39 million sperms per ejaculate and 15 million per ml of semen with 58% vitality, 32% progressive motility and 40% total motility and 4% morphologically normal forms [22].

Normally oligozoospermia and 13 % of azoospermia with defective spermatogenesis are linked to defects of the Y chromosome – Y chromosome microdeletion in *AZF* region [24]. Any morphological change in sperm is also likely to have adverse effect on its functional efficiency. Empirical evidences indicate that double headed sperms, sperms having defective tail or dysfunctional acrosome or other morphological defects are incapable to take part in fertilization process. Morphological abnormality of sperm (tetratozoospermia) and insufficient sperm motility (asthenozoospermia) are some of the aspects of infertility. The combination of them can also occur, out of which oligoasthenoteratozoospermia (OAT) is most frequent [25]. Approximately 30% of OAT infertile men are diagnosed as idiopathic [26].

Idiopathic oligoasthenoteratozoospermia (iOAT) is defined as defective spermatogenesis of unknown etiology and is regarded as undetectable by the common laboratory methods[27]. Mast cells releasing inflammatory mediators are reported to directly suppress sperm motility in a potentially reversible manner, and may be a common pathophysiological mechanism for several factors responsible for infertility[28]. Any of the factors described below or combination of them can result into abnormal changes into quality and quantity of semen and sperm within it. The reason behind unpredictable exact cause is that the terms used to describe semen-analysis abnormalities have overlapping definitions and are often misinterpreted which needs better science technologies; the better course is to discard these indistinct and difficult labels and simply report semen analyses quantitatively [29].

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. Hormonal factors work in a mutually interacting circuit wherein they have self-limiting effects on their own rates of manufacture and secretion.

In fact, most of the hormones operate by means of a negative feedback mechanism. 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. Testosterone deficiency leads to a clinical condition called as hypogonadism. The abnormalities such as reduced sperm production and fertilizing capability occur in male reproductive system due to irregular action of androgen during development [30].

Recent researchers have indicated that copious quantities of circulating estrogens may suppress the spermatogenesis and adversely affect the male fertility power. Germ cell tumors produce β–human chorionic gonadotropin (β-HCG) and α-fetoprotein (AFP). The increased level of β-HCG of intratesticular estradiol production decreases or impairs spermatogenesis in the contralateral testis [31] while increased level of AFP decreases total sperm countoligozoospermia [32] Moreover, it has been found that the patients suffering from germ cell tumors had an increased level of serum follicle stimulating hormone (FSH), a rare cause of treatable male infertility.

A recent research has suggested that administration of clomiphene citrate; hCG and hMG to non-obstructive azoospermic patients can results in an increased level of FSH, and total testosterone level and thus the rate of sperm in the ejaculate [33]. Plasma SHBG (sex hormone-binding globulin) levels tended to be lower in idiopathic infertile men (OAT) compared to normal fertile men; affecting sperm count, motility and 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 [18].

No therapeutic measures for obesityassociated male infertility have been studied yet. Thus, greater clinical awareness is needed for understanding its mechanism and treatment.

Receptor Dysfunction and defect in biosignalling pathways also contribute to male infertility problem. In several cases, development and organization of male gonadal organs are affected by faulty receptors mediating the biosignalling pathway of sex steroids. 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. A defective receptor is not able to mediate the function of testosterone and these results into the development of the clinical condition known as testicular feminization or androgen insensitivity which may be considered as a factor of male infertility. According to a research paper, insufficient androgen and FSH signaling are unable to respond to an endogenous hormonal milieu that stimulates the initiation of spermatogenesis and may be responsible for the azoospermia of the infantile primate testes [34].

Anatomical Abnormalities: Various disorders in different male reproductive organs might cause testicular or post-testicular abolition of fertility. In industrialized 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 [35]. 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 fertility (33% to 66%) and testicular cancer, 5-10 times greater than normal[36]. Mutations in insulin-like factor 3 gene, its receptor gene and androgen receptor gene explain a minor reason of cryptorchidism [37] presented a report in support of intrauterine environment and maternal inheritance contributing to the phenomenon of cryptorchidism.

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 [35]. 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[38]. 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 [39].

Chromosomal abnormalities in patients with cryptorchidism and hypospadias have been reported [40]. Varicocele, another abnormality is a collection of abnormally dilated, swelled spermatic veins that drain the testicle. It can occur on both side, but most frequent on the left side. A clinical varicocele is found in about 15% of all adult males[41]. Varicocele can lower sperm quality and quantity, and even testicles may shrink. In addition, epididymitis, anomalies of seminal vesicle and tubular damage/dysfunction due to infection may contribute to male infertility. Congenital anomalies may be either infrequent, with a localized defect in the proximal part of the vas deferens, or an inclusive abnormal development [42].

Hendry *et al.* investigated 370 azoospermic males with normal serum FSH levels and observed 5% unilateral absence of the vas deferens and 18% bilateral absence. Inherited deformities of the penis can deflect the ejaculate and prevent it from emerging at the tip of the penis [43]. Epispadias is a type of congenital defect with shorter, wider size and abnormal curvature which can make successful sexual intercourse difficult. It can be surgically corrected and pregnancies may be produced [44]. Epididymitis is caused due to inflammation of the epididymis which can progress to acute and chronic forms. Anomalies of the seminal vesicles can be categorized into abnormalities of number (agenesis, fusion), canalization (cysts) and maturation (hypoplasia) [45].

Chemical / Occupational 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 that has exposed man to umpteen numbers of chemicals which were not even in thought for decades ago. There are many chemicals that can temporarily or permanently affect the fertility of men either by altering spermatogenesis, sperm parameters or hormonal imbalance. The infertility problem in patients seeking infertility treatment may frequently be due to the chemical occupational exposures [46]. Among such chemicals are lead [47], diaminostilbene [48], benzo(a)pyrene (BaP) [49], dibromochloropropane [50], carbon disulphide [51] ,alkyl mercury [52], ethylene glycol ether [53],methylene chloride [54], manganese [55], carbaryl [56] and vinyl chloride [57].

Prenatal diethylstilbestrol (DES) exposure may slightly increase the risk of infertility, but does not affect the number of fathered pregnancies or live births [58]. Sulfasalazine might cause male infertility by inducing oxidative stress [59]. Among heavy metals, lead was first to be reported to have antifertility effect. Moderate exposure to lead and cadmium can decrease semen quality [60]. Exposure to copper can result into oligoteratozoospermia and asthenozoospermia[61]. In human studies [62] observed reduced sperm quality in welders exposed to chromium. The nematocide dibromodichloropropane (DBCP) have negative effect on spermatogenesis [63]. Ethane 1,2-dimetane sulphonate (EDS) cause toxicity to Leydig cells as a result of lack of plasma testosterone level [64]. Boric acid is also a reproductive toxicant which reduces the testosterone level [65]. Chromium compounds mainly cause testicular tissue damage by increasing oxidative stress [66]. Aluminium causes reduced weight of reproductive organs and impair fertility [67]. Ammonium metavanadate is reported to have toxic effect on reproduction and fertility [68].

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, dichloro-diphenyldichloroethylene (p,p′-DDE), restricted to intra-uterine and thus undetected in subfertile men [69]. 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 [70]. Pesticides affect the particular stages of reproduction, mainly the prenatal stage and results in damage to the reproductive organs and ultimately impair fertility [71]. Prenatal exposure of phthalates in the womb of human adversely affects male reproductive system and impairs testicular functions [72].

Many pesticides particularly persistent organic pollutants (POP) i.e. nonmetabolic 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 affecting post-testicular sperm through the mechanism of decrease in the metabolism of glucose to CO2 by epididymal ejaculated sperm [73].

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* mechanism of protein phosphorylation [74]. 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 [75].

Genetic / Congenital Factors: A gene is a molecular hereditary unit of living organisms that occupies a specific location on a chromosome as a sequence of DNA and holds the information to build and maintain an organism cell and pass genetic traits to offsprings. 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. 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 [76].

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 due to 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 [77].

The gene CREM and ACT have regulatory functions in human spermatogenesis and help to understand its molecular mechanisms [78]. 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 [79] reported that XPA (–4) G/A polymorphism in XPA promoter of nucleotide-excision repair (NER) pathway lowers the transcriptional activity and increases sperm DNA damage and thus may contribute to male infertility.

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[80]. It has been recently reported by[81] 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.

Safarinejad *et al* [82] has investigated the association of the (TAAAA)*n* repeat and Asp237Asn polymorphisms in 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 [83].

Some genetic problems with chromosomes occur in about 2 to 20% of infertile men and can affect their fertility in two ways-

(i) Male sex partner having chromosomal abnormalities can disrupt cell division and sperm production, and

(ii) 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 [84]. However, in the case of genetic infertility, the molecular mechanisms of spermatogenic damage (for example Yq microdeletions) are still not known. 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 AZFa, b or c region cause genetic abnormalities and eventually male infertility [85].

Mutations in the genes responsible for fertility lead to defects in development of the germ cell lineage that causes infertility. This type of infertility can be repaired *via* increased frequency of mutations in DNA of infertile males with meiotic arrest[86]. 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 SHBG, luteinizing hormone (LH) and values for sperm density, sperm motility, and percentage of sperm with normal morphology[87]. However, further researches are needed to establish better association between the biological mechanism of ESR-α, and ER-β and incidence of male infertility.

Alcoholism, Smoking and Club Drug Usage: 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, within 3 months, alcohol withdrawal allowed fast and drastic improvement of the semen parameters to normal [88].

Sperm concentration, percentage motility, morphology, and percentage viability are significantly affected due to tobacco chewing in Indian men that lead to infertility [89]. 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, fertilizing capacity of spermatozoa through increased seminal oxidative stress, DNA damage and lower implantation rates of embryos, correlated with cigarette smoking/day and smoking duration [90]. In addition to above, there are increased seminal leucocytes, oval sperm percentage, defective head-piece spermatozoa and spermatozoa with cytoplasmic droplets in smokers [91, 92].

Moreover, it decreases the antioxidant activity of superoxide dismutase and increases leucocytospermia which adversely affect sperm motility[93] but the negative impact of smoking on intracellular antioxidant enzymes does not increase oxidative DNA damage [94]. Nicotine, the main constituent of smoke has a significant impact on sperm morphology and sperm count [95]. Consumption of more than 20 cigarettes/day shows elevated seminal cadmium (Cd) level in smokers [96].

Smoking has negative correlation between cadmium in blood and sperm density [97]. Also, lead in seminal plasma affects fertility of men [98]. Besides 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 [99]. On analyzing the degree of DNA fragmentation in spermatozoa using the TUNEL-assay with flow cytometry detection, it was found to be higher in smokers concluding that smoking may have negative impact on sperm nuclear quality [100].

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 [101]. Even male cigarette smoking can significantly decreased live birth rates[102]. However, further studies are required to establish this beyond reasonable doubts.

Another serious negative factor is use of club drugs, pharmacologically heterogeneous group of psychoactive drugs that tend to be abuse by teenagers and young adults at bars, nightclubs, concerts and parties. These drugs vary by country and region. Ecasty (MDMA), gamma-hydroxybutyrate (GHB), ketamine, methamphetamine, rohypnol, marijuana, caffeine, heroin, morphine, poppers, and cocaine are some examples of such drugs that are increasing in popularity as a part of western lifestyle [103] and these addictions are responsible for deleterious effects on entire sperm structure [104].

A study explore the people who use marijuana weekly or who exposed to marijuana since adolescents, and examined them to had twice the testicular deficiencies, erectile dysfunction, infertility anomalies and cancer risk when compared to men who smoked a couple of times and those who never smoked marijuana [105]. Its continuous use reduces sperm quality and testosterone level and increase impotence [106]. Delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, can impair sperm functions and adversely affect male fertility [107]. The addiction of heroin and methadone result into asthenospermia (100%), teratospermia & hypospermia (24%) and oligozoospermia (17%) [108].

A study analyzed the semen of 40 years old man who had been addicted to heroin, morphine, hashish, and other narcotics for 12 years and 2 years after self-denial from drugs and revealed oligozoospermia, asthenozoospermia, and morphologically abnormal spermatozoa [109]. Chronic intake of cocaine has a deleterious effect on spermatogenesis and fertility [110]. Cocaine cause reproductive system injury and may involve Fasmediated apoptosis [111]. Cocaine induced testicular injury which could be related to apoptosis [112] and may involve Fas-mediated mediated pathway [111] or mitochondria-associated pathway[113]. Cocaine exposure appears to involve the release of cytochrome c from mitochondria and its subsequent activation of caspase 9 and caspase 3 in testes and play a key role in cocaine-induced testicular germ cell loss/apoptosis [113, 114].

Lifestyle, Nutrition & Diet Factors: In recent years, a number of lifestyle factors have been suggested which may be adversely affecting the male fertility. Unhealthy and imbalanced lifestyle can aid the risk of impotency in males. Desk bound work, tight clothing, composition of diet and keeping mobile phones close to scrotum may have adverse effects on male fertility. The decreased human semen quality over recent decades may be related to a change in living habits, illustrated by a more deskbound work with high energy intake and increased incidence of obesity [115]. However it is still unclear 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 [116]. The oral administration of antioxidants (vitamins C and E, zinc, selenium, folate, carnitine and carotenoids) in infertile men could improve sperm quality and pregnancy rates [117] but no particular antioxidant is able to improve fertilization rate in infertile men, whereas a combination of them provide a better effect [118]. The high intake of dietary antioxidants-vitamin C, vitamin E, β-carotene, folic acid, zinc, papaya, lactoferrin and lipophilic foods improve the semen parameters [119, 120, 121].

Low intake or deficiency of these nutrients cause poor semen quality and increases the risk of male infertility [122]. Long term use of isoflavone phytoestrogens containing soybean have adverse effect on the development and function of the male reproductive system resulting into decrease in sperm count and fertility [123]. Carnitine, a water-soluble antioxidant derived from the human diet provides the primary fuel for sperm motility and protect sperm DNA from ROS-induced damage and apoptosis [124]. Patients with defective sperm motility have a reduced Lacetylcarnitine/ L-carnitine ratio [125]. However, its oral supplementation improves the motility of spermatozoa [126].

Human studies have shown direct relationship between obesity and infertility [127] demonstrated that diet induced obesity in male mice cause a significant reduction in fertility. Obesity resulted in reduced number of plugs and pregnancies of control females paired with obese versus lean males. Neither the reversibility of infertility associated with obesity with weight loss nor effective therapeutic interventions have been known till time.

However, contradictory results have been reported on obesity associated male infertility. A decreased sperm count and volume of ejaculation had been reported in men with increasing body mass index (BMI) and no correlation with sperm concentration, motility and morphology [128] while contrast papers had reported a negative correlation between BMI and sperm count and concentration [129].

Hofny and Hammoud reported positive correlation between BMI and abnormal sperm morphology[130] and sperm count[131]**.** According to a recent paper obesity may induce oxidative stress and decrease testosterone levels which may alter testicular functions and thus concluding that obesity can be an important factor in the etiology of the male infertility [132]. High blood pressure is another condition that affects impotency and is a result of poor lifestyle choices. This may be because of increased pressure which may damage small vessels in the penis or that hormonal levels are affected. Added weight, lack of exercise, unhealthy or high-sodium diet and alcohol; all contribute to high blood pressure.

Wdowiak *et al* (2007) [133] 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[134]. The radio-frequency electromagnetic waves (EMW) from these devices decreases sperm count, motility, viability and morphology leading to poor sperm quality [135] depending upon the daily exposure time period to it [136].

Ageing: The effect of age on male fertility is not clear. However, evidence is growing that the genetic quality of sperm, its concentration and motility typically decreases with age. According to a research paper, increasing male age cause decline in semen volume, sperm motility, and sperm morphology but not sperm concentration [137]. Recently, a paper evaluating the impact of age on the expression of apoptotic biomarkers in human spermatozoa provided the evidence that increasing male age is associated with reduced sperm concentration [138]. The decrease in fertility with age is associated with a decline in testicular weight, sperm production and the testosterone levels [139]. A research presented the evidence of age-related increase in the number of sperm with chromosomal breaks and fragments (ie. structural chromosomal aberrations in sperm) which have significant effects on the viability and genetic health of human pregnancies and offspring [140]. Vagnini L. *et al* [141] investigated the influence of age on sperm DNA damage. They demonstrated a significant increase in sperm DNA fragmentation index (DFI) with age. With TUNEL assay they showed an increase in sperm DNA damage with age.

Oxidative Stress and Reactive Oxygen Species: Reactive oxygen species (ROS) are highly reactive oxidizing agents belonging to the class of free radicals. ROS generated within semen are believed to play both sperm pathological and physiological role in male fertility [142] facilitating capacitation, hyperactivation, acrosome reaction, motility, fertilization, sperm-oocyte fusion [143]. However, ROS-induced sperm damage is considered as the primary basis for impaired fertility [144]. Its high concentration causes altered sperm pathology through intracellular ATP depletion leading to insufficient axonemal phosphorylation, lipid peroxidation, decreased motility, and viability and increased morphology defects with deleterious effects on sperm capacitation and acrosome reaction [145] and have been implicated in prostate cancer [146]. The increased levels of malondialdehyde, nitric oxide and decreased levels of zinc and superoxide also play a role in disruption of spermatozoa membrane integrity and reduction of sperm DNA integrity [147].

Oxidative stress has been considered a major contributory factor for ROS-induced male infertility [148]. It takes place due to imbalance between ROS and total antioxidant capacity (TAC) within the body and leads to sperm damage, deformity and eventually male infertility [149]. Oxidative stress induced lipid peroxidation also damage sperm membrane affecting its fluidity and motility [150] as spermatozoa are rich in polyunsaturated fatty acids, which are susceptible to ROS.

Leuckocytes (mainly macrophages and neutrophils) and immature spermatozoa are the main source of excessive ROS production, leading to sperm dysfunction [151, 152, 153]. When pathogens invade the human body, it produces polymorphonuclear leukocytes and macrophages which generate ROS and lead to sperm damage [154]. Prostatitis, and accessory gland infection increases oxidative stress and results into excessive damage to spermatozoa [155].

ROS may promote apoptosis, the mechanism to remove old, senescent and destructive cells from the body [156] ,which can cause numerous forms of sperm DNA damage, e.g. chromatin cross-linking, chromosome deletion, DNA strand breaks and base oxidation, mutations, and other lethal genetic effects [157], leading to decreased sperm concentration [158] and other physiological and pathological changes. As the regulated caspase cascade plays a critical role in sperm differentiation, testicular maturation; ROS and higher levels of cytochrome c, caspases 9 and 3 generated in apoptotic pathway causes increased sperm damage [159] and thus can be associated with multiple andrological pathologies – impaired spermatogenesis, membrane integrity, decreased sperm motility, increased levels of sperm DNA fragmentation- single and double DNA strand breaks, testicular torsion, varicocele and immunological infertility[160,161,162,163]. Thus, seminal oxidative stress, ROS, apoptosis and sperm DNA damage are interconnected, and eventually results into infertility problems.

Pollution and Radiation: The different types of pollution such as air, water, land, sound and radioactive affects the human beings in many ways by causing adverse effects to their body organs and thus leading to serious diseases. Air pollution is associated with reduced sperm motility, two to three months after exposure [164]. According to a finding diesel exhaust particles (DEP) suppress expression of sex steroid hormone receptors (ER-α) in TM3 mouse Leydig cells by approximately 50% [165].

Continuous exposure to traffic pollutants impairs sperm quality and reduced fertility in young and middle-aged men. A study for the first time found a new group of anti-androgen chemicals affecting wildlife including humans which when enter into the water system may cause reproductive problems - reduced breeding capability and feminizing effects in male fish. A research team investigated that untreated (influent) and treated (effluent) textile dye wastewaters cause decrease in body weight (7–25%) and reproductive organ weight (testis, epididymis, prostate gland and seminal vesicle, 2–48%), total protein (14–70%), cholesterol (14–91%) and total lipid (10–30%) content of reproductive organs and spermatozoa, and for fructose levels in seminal vesicle (18–44%). Histopathological examination revealed altered spermatogenesis along with higher sperm abnormalities, reduced sperm counts (10–59%) and altered motility (14–56%) [166]. Similar research on pulp and paper-mill effluents showed reduction in the relative weight of the testis, decline in total sperm count, motility, testosterone level and a drop in the activity of epididymal α-glucosidase[167]. This factor may be related with increasing male infertility caused by TDS but no stronger evidence has been reported yet.

In recent years, researches have shown that ozone produced as a secondary pollutant in the troposphere compartment of the atmosphere reduces sperm quality, sperm density in semen and adversely affects male fertility through oxidative damage pathway as it is a powerful oxidant; indicating ozone may be a reproductive toxicant[168]. A large number of researches have been done on the adverse effects of radiation on male and female reproductive systems.

The 10-GHz microwave radiation has negative impact on the reproductive system which causes infertility [169]. Radiofrequency electromagnetic waves (RF-EMW) emitted from cell phones may lead to oxidative stress in human semen which negatively affect spermatozoa and impair male fertility [170]. Radiation may have effects on male and female reproductive organs, hypothalamus–pituitary–gonadal axis and on genetic aspects [171].

Diseases: There are several general medical disorders or conditions that may reduce male fertility. Mumps, tuberculosis and sexually transmitted diseases can affect sperm production by causing inflammation and obstruction in the male genital tract. 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 genitourinary tract [172].

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. The infectious process may deteriorate spermatogenesis, impair sperm function and obstruct seminal tract.

Chlamydia trachomatis and *Nisseria gonorrhoeae* are the most common microorganisms while *Escherichia coli* being less frequent affecting male fertility [172]. *Chlamydia* infection impairs sperm parameters, proportion of DNA fragmentation, and acrosome reaction capacity which may adversely affect male fertility [173]. 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 few weeks. Febrile illness episode to a fertile man cause temporary decrease in total sperm count, percentage motility and viability, and increased DNA fragmentation DNA stainability, representing marked effects on semen parameters and sperm DNA integrity [174].

Diabetes is another medical pathology which can cause problems with erection and ejaculation. 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 autonomous nervous system get damaged which results in problems associated with erection and ejaculation. It has a direct effect on fertility causing DNA damage in sperm. Moreover, the occurrence of primary and secondary infertility was significantly higher in diabetic men as compared to non-diabetic men providing strong evidence of diabetes induced male infertility [175].

Neurological disorders such as multiple sclerosis, stroke and spinal cord injury and disease can cause problems with erection and ejaculation. Cancers affecting the genital tract and endocrine system may directly decrease male fertility. Chemotherapies and radiation used for treating cancer may severely affect sperm production or even stop it. Many forms of stress can affect fertility and reproduction and cause changes in the body at hormonal level.

Mild-to-severe emotional stress and psycho-pharmacologic agents may reduce testosterone levels and possibly interrupts with spermatogenesis in men. Infertility measurement and treatment can lead to pain and negatively affect sperm samples [176]. 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. In some men, depression may be linked to heart disease and erectile dysfunction. ROS-induced oxidative stress within semen, damage sperm membrane which further reduce sperm motility and ability to fuse with oocyte. Moreover, it also destroys sperm DNA integrity, compromising the paternal genomic contribution to the embryo[177].

Drugs: Studies have shown that many drugs used to treat 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. A group of drugs-calcium channel blockers (CCB) are typically prescribed for patients of hypertension as they increase the amount of blood and oxygen supply to heart helping to minimize its work. However, they interfere with the fertilization process by preventing the sperm from being able to penetrate an egg and are commonly associated with male infertility. Long term administration of such drugs suppress spermatogenesis as many sperm functions such as motility[178], hyperactivity[179], acrosome reaction[180] and capacitation[181] are regulated by cytoplasmic calcium. Previous papers had also reported that the effect of CCBs get reverse on the withdrawn on the drug[182].

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. Major classes of antibiotics have significant negative impact on spermatogenesis or spermatozoal functions. Some of the antibiotics that are known or suspected to interfere with male fertility [183] (**Table no. 1).**

Antibiotic	Use	Effects
Nitrofurantoin	Urinary tract infections	Reduced sperm count
Neomycin	Bacterial infections	Reduced sperm production and motility
Macrolides	Legionnaires disease	Reduced sperm motility

Sulfasalazine	Rheumatoid arthritis, Ulcerative colitis	Reduced sperm count, motility and abnormal Morphology
Ketoconazole	Fungal infections	Reduced sperm count

Chemotherapy: The chemotherapeutic measures such as drugs and radiation often used for the treatment of cancer result in decrease in sperm count and motility and severely reduce sperm production (oligozoospermia) and even lead to azoospermia. These effects can be temporary or permanent.

Plants: There are several commonly used plants that are reported with antifertility properties. Different plants affect male reproduction by different ways: impair testicular functions, suppress spermatogenesis, hinder Leydig cells function and steroidogenesis and reduce hormone production[184]. The leaf powder of *Azadirachta indica* (neem) causes reversible histological and biochemical changes in testes[185] and the aqueous extract of old and tender neem leaves is a potent spermicide[186]. According to another study neem causes marked structural and functional alteration in testes, epididymis and seminal vesicle and reverse after cessation of its use [187]. It causes significant decreases in epididymal sperm counts, serum testosterone levels and increases in sperm head abnormality and subsequently the quality and quantity of spermatozoa [188]. Chloroform extract of *Carica papaya* seeds induces long-term reversible azoospermia[189]. Its aqueous extract has a significant dose dependent suppressive affect on cauda epididymal sperm motility with reduction in sperm count and viability which completely restore on its withdrawn[190]. *Momordica charantia* seed have antispermatogenic, antisteroidogenic and androgenic properties[191]. It causes dose dependent significant decline in sperm number, motility, testicular testosterone concentrations and testicular volume leading to suppress sperm production[192] and reversible histological alterations in the prostate and testes [193].

Indian Status: Census of 1981 estimated infertility around 4-6% in India [194]. Nearly 50% of infertility is related to reproductive abnormalities or disorders in male [195]. However, in 25% of cases from India, their causal factors are failed to be detected are categorized under unexplained infertility [196]. Danadevi *et al* (2003) [197] found significant decrease sperm motility, morphology and semen abnormalities of 57 south Indian welders occupationally exposed to welding fumes of nickel and chromium. A similar research paper reported significant higher numbers of morphologically abnormal sperms in 61 industrial workers occupationally exposed to chromium, 53% of which showed less than 30% normal form of sperm [198]. According to a survey from 1993 to 2005, sperm density, morphology and sperm motility are deteriorating in the southern part of India [199]. Mukhopadhyay *et al* (2009) [200] reported a significant decline in the sperm motility and volume between two decades (1980s and 2000s) and the age related changes in semen parameters of 3729 male of Kolkata city.

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. The present review has revealed many factors that are responsible for male infertility. Some cases are due to anatomical abnormalities such as cryptorchidism, hormone imbalance and genetic defects but for many factors humans themselves are responsible, such as harmful environmental exposures, irregular lifestyle, improper diet and addiction to alcohol and smoke. Several recent studies have focused on the impact of free radicals and role of antioxidants on male fertility. 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 and stressful lifestyles etc. which play a major role in leading to infertility. In addition to above factors, several plants are also reported to have harmful effects on reproductive system. Thus, future research should be directed towards studying the toxic effects of all the factors including plants and drugs and the detailed mechanism of their action should also be elucidated. 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 Authorization 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.

REFERENCES:

1. Purvis K, Christiansen E: Male infertility: Current concepts. Ann Med 1992; 24: 259-272.
2. World Health Organization (WHO), Infertility: A Tabulation of Available Data on Prevalence of Primary and Secondary Infertility. WHO/MCH/91.9 World Health Organization, Geneva 1991.
3. Benshushan A, Shoshani O, Paltiel O, Schenker JG, Lewin A: Is there really a decrease in sperm parameters among healthy young men? A survey of sperm donations during15 years. J Assist Reprod Genet 1997; 14(6): 347-53.
4. Feki NC, Abid N, Rebai A, Sellami A, Ben Ayed B, Guermazi M, Bahloul A, Rebai T, Ammar LK: Semen quality decline among men in infertile relationships: Experience over 12 Years in the South of Tunisia. J Androl 2009; 30(5): 541-547.
5. Huang CY, Yao CJ, Wang C, Jiang JK, Chen G: Changes of semen quality in Chinese fertile men from 1985 to 2008. Zhonghua Nan Ke Xue 2010; 16(8): 684-648.
6. Jørgensen N, Joensen UN, Jensen TK, Jensen MB, Almstrup K, Olesen IA, Juul A, Andersson AM, Carlsen E, Petersen JH, Toppari J, Skakkebaek NE: Human semen quality in the new millennium: a prospective crosssectional population-based study of 4867 men. BMJ Open 2012; e000990: 1-13.
7. Auger J, Jouannet P: Federation Francaise de CECOS, Evidence for regional differences of semen quality among fertile French men. Hum Reprod 1997; 12; 740–745.
8. Swan SH, Brazil C, Drobnis EZ, Liu F, Kruse RL, Hatch M, Redmon JB, Wang C, Overstreet JW: Geographic differences in semen quality of fertile US males. Environ Health Perspect 2003; 111: 414–420.
9. Chia VM, Quraishi SM, Devesa SS, Purdue MP, Cook MB, McGlynn A: International trends in the incidence of testicular cancer, 1973–2002. Cancer Epidemiol Biomarkers Prev 2010; 19: 1151–1159.
10. Paasch U, Salzbrunn A, Glander HJ, Plambeck K, Salzbrunn H, Grunewald S, Stucke J, Vierula M, Skakkebæk NE, Jørgensen N: Semen quality in sub-fertile range for a significant proportion of young men from the general German population: a co-ordinated, controlled study of 791 men from Hamburg and Leipzig. Int J Androl 2008; 3: 93–102.
11. Philipov D, Kohler HP: Tempo Effects in the fertility decline in Eastern Europe: Evidence from Bulgaria, the Czech Republic, Hungary, Poland and Russia. European J Population 2000; 17(1): 37-60.
12. Denrose LF, Ezeh AC: Men's influence on the onset kind progress of fertility decline in Ghana, 1998-1999. Population Studies 2005; 59(2): 197-210.
13. Moultrie T, Timaeus I: The South African fertility decline. Evidence from two censuses and a demographic and health survey. Population Studies 2003; 57(3): 265-283.
14. Basu A: Fertility decline and worsening gender bias in India: Is Kerala no longer an Exception? Development and Change. 2000; 31(3): 1093-1095.
15. Anand Kumar TC: *In-vitro* fertilization in India. Curr Sc 2004; 86(2): 254-256.
16. Isidori AM, Pozza C, Gianfrilli D, Isidori A: Medical treatment to improve sperm quality. Repro BioMed Online 2006; 12(6): 704-714.
17. Brugo-Olmedo S, Chllik C, Kopelman S: Definition and causes of infertility. Reprod BioMed Online 2008; 2(1): 41-53.
18. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT: Impact of male obesity on infertility: a critical review of the current literature. Fertil Steril 2008a; 90(4): 897-904.
19. Olayemi FO: A review on some causes of male infertility. Afr J Biotechnol 2010; 9(20): 2834-2842.
20. Saradha B, Mathur PP: Effect of environmental contaminants on male reproduction. Environ Toxicol Pharmacol 2006; 21(1): 34-41.
21. Saacke RG, Nadir S, Nebel RL: Relationship of semen quality to sperm transport, fertilization, and embryo quality in ruminants. Theriogenology 1994; 41(1): 45-50.
22. Kishore Kumar P, Raju AB: A review on male fertility. Hygeia J Med 2011; 3(1): 20-28.
23. Cooper TG, Noonan E, Von Eckardstein S, Auger J, Baker HWG, Behre HM, Haugen TB, Kruger T, Wang C, Mbizvo M, Vogelsong KM: World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010; 16 (3): 231–245.
24. Soares AR, Costa P, Silva J, Sousa M, Barros A, Fernandes S: AZFb microdeletions and oligozoospermia--which mechanisms? Fertil Steril 2012; 97(4): 858-863.
25. Isidori A, Latini M, Romanelli F: Treatment of male infertility. Contraception 2005; 72(4): 314-318.
26. Cavallini G: Male idiopathic oligoasthenoterato-zoospermia. Asian J Androl 2006; 8(2): 143-157.
27. Bonanomi N, Lucente G, Silvestrini B: Male fertility: core chemical structure in pharmacological research. Contraception 2002; 65: 317–320.
28. Menzies FM, Shepherd MC, Nibbs RJ, Nelson SM: The role of mast cells and their mediators in reproduction, pregnancy and labour. Hum Reprod Update 2010; 17 (3): 383–396.
29. Grimes DA, Lopez LM: Oligozoospermia "azoospermia," and other semen-analysis terminology: the need for better science. Fertil Steril 2007; 88(6): 1491-1494.
30. Sikka SC, Gurbuz N: Reproductive toxicity of organophosphate and carbamate pesticides. Toxicol Organophos Carb Comp 2006: 447-462.
31. de Bruin D, de Jong IJ, Arts EG, Nuver J, Dullaart RP, Sluiter WJ, Hoekstra HJ, Sleijfer DT, Gietema JA: Semen quality in men with disseminated testicular cancer: relation with human chorionic gonadotropin beta-subunit and pituitary gonadal hormones. Fertil Steril 2009; 91(6): 2481-2486.
32. Hansen PV, Trykker J, Andersen J, Helkjaer PE: Germ cell function and hormonal status in patients with testicular cancer. Cancer 1989; 64(4): 956–961.
33. Hussein A, Ozgok, Y, Ross L, Rao P, Niederberger C: Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int (In Press) 2012.
34. Majumdar SS, Sarda K, Bhattacharya I, and Plant TM: Insufficient androgen and FSH signaling may be responsible for the azoospermia of the infantile primate testes despite exposure to an adult-like hormonal milieu. Hum Reprod 2012; 27(8): 2515-2525.
35. Hutson JM, Balic A, Nation T, Southwell B: Cryptorchidism. Semin Pediatr Surg 2010; 19(3): 215-224.
36. Robin G, Boitrelle F, Marcelli F, Colin P, Leroy-Martin B, Mitchell V, Dewailly D, Rigot JM: Cryptorchidie: de la physiopathologie a infertilite. Gynecol Obstet Fertil 2010; 38(10): 588-599.
37. Jensen MS, Toft G, Thulstrup AM, Henriksen TB, Olsen J, Christensen K, Bonde JP: Cryptorchidism: concordancein

monozygoticand dizygotic twin brothers, full brothers and half-brothers. Fertil Steril 2010; 93(1): 124-129.
38. Wood HM, Ejder JS: Cryptorchidism and testicular cancer: separating fact from fiction. J Urol 2009; 181(2): 452-461.
39. Thorup J, McLachlan R, Cortes D, Nation TR, Balic A, Southwell BR, Hutson JM: What is new in cryptorchidism and hypospadias—a critical review on the testicular dysgenesis hypothesis. J Pedia Surg 2010; 45(10): 2074-2086.
40. Moreno-Garcia M, Miranda EB: Chromosomal anomalies in cryptorchidism and hypospadias. J Urol 2002; 168(5): 2170-2172.
41. Baazeem A, Belzile E, Ciampi A, Dohle G, Jarvi K, Salonia A, Weidner W, Zini A: Varicocele and male factor infertility treatment: a new meta-analysis and review of the role of varicocele repair. Eur Urol 2011; 60: 796-808.
42. Schlegel PN, Shin D, Goldstein M: Urogenital anomalies in men with congenital absence of the vas deferens. J Urol 1996; 155: 1644–1648.
43. Hendry WF: Disorders of ejaculation: congenital, acquired and functional. Br J Urol 1998; 82: 331–341.
44. Woodhouse CRJ, Ransley PG, Williams DI: The patient with exstrophy in adult life. Br J Urol 1983; 55: 632–635.
45. Patel B, Gujral S, Jefeerson K, Evans S, Persad R: Seminal vesicle cysts and associated anomalies. BJU Int 2002; 90: 265–271.
46. Mendiola J, Torres-Cantero AM, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S, Bernabeu R: Exposure to environmental toxins in males seeking infertility treatment: a case-controlled study. Reprod BioMed Online 2008; 16(6): 842-850.
47. Cullen MR, Kayne RD, Robins JM: Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. Arch Environ Health 1984; 39: 431.
48. Landrigan PJ, Melius JM, Rosenberg MJ, Coye MJ, Binkin NJ: Reproductive research Scand J Work Environ Health 1983; 9: 83-88.
49. Inyang F, Ramesh A, Kopsombut P, Niaz MS, Hood DB, Nyanda AM, Archibong AE: Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. Reprod Toxicol 2003; 17(5): 527-537.
50. Whorton MD, Krauss RM, Marshall S, Milby TH: Infertility in male pesticide workers. Lancet 1977: 1259-1266.
51. Wagar G, Tolonen M, Stenman UH, Helpio E: Endocrinologic studies in men exposed occupationally to carbon disulfide. J Toxicol Environ Health 1981; 7: 363-371.
52. Henderson J, Rennie GC, Baker HWG: Association between occupational group and sperm concentrations in infertile men. Clin Reprod Fertil 1986; 4(4): 275-281.
53. Welch L, Schrader S, Turnei T, Cullen MR: Effects of exposure to ethylene glycol ethers on shipyard painters: II. Male reproduction. Am J Ind Med 1988; 14: 509-526.
54. Kelly M: Case reports of individuals with oligospermia and methylene chloride exposures. Reprod Toxicol 1988; 2: 13-17.
55. Lauwerys R, Roels H, Genet P, Toussaint G, Bouckaert A, Cooman S: Fertility of male workers exposed to mercury vapour or to manganese dust: a questionnaire study. Am J Ind Med 1985; 7: 171.
56. Wyrobek AJ, Watchmaker G, Gordon L, Wong K, Moore D, Whorton D: Sperm shape abnormalities in carbaryl-exposed employees. Environ Health Perspect 1981; 40: 255-265.
57. Makarov IA. Sexual disorders of male workers occupationally exposed to ethylmetacrylate and vinyl chloride: Gig Ti Prof Zabol 1984; 6: 19-23.
58. Perez KM, Ernstoff LT, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN: National Cancer Institute's DES Follow-up Study Group, Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. Fertil Steril 2005; 84(6): 1649-1656.
59. Alonso V, Linares V, Belles M, Albina ML, Sirvent JJ, Domingo JL, Sánchez DJ: Sulfasalazine induced oxidative stress: A possible mechanism of male infertility. Reprod Toxicol 2009; 27(1): 35-40.
60. Telisman S, Cvitkovic P, Jurasovic J, Pizent A, Gavella M, Rocić B: Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadium, zinc and copper in men. Environ Health Perspect 2000; 108: 45-53.
61. Lahdetie J: Occupation and exposure-related studies on human sperm. J Occup Environ Med 1995; 37: 922-930.
62. Mortensen JT: Risk for reduced sperm quality among metal workers, with special reference to welders. Scand J Work Environ Health 1988; 14: 27-30.
63. Rees TJ: The toxicology of male reproduction. A literature review in applied toxicology. MS Thesis Portsmouth University. 1993.
64. Sprando RL, Santulli R, Awoniyi CA, Ewing LL, Zirkin BR: Does ethane 1,2- dimethanesulphonate (EDS) have a direct cytotoxic effect on the seminiferous epithelium of the rat testis. J Androl 1990; 92: 353-360.
65. Fail PA, George JD, Seely JC: Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fundam Appl Toxicol 1991; 17: 225-239.
66. Acharya UR, Mishra M, Mishra I, Tripathy RR: Potential role of vitamins in chromium induced spermatogenesis in swiss mice. Environ Toxicol Pharmacol 2004; 15: 53-59.
67. Guo CH, Lu YF, Wang Hsu GS: The influence of aluminum exposure on male reproduction and offspring in mice. Environ Toxicol Pharmacol 2005; 20: 135-141.
68. Morgan AM, El-Tawil OS: Effects of ammonium metavanadate on fertility and reproductive performance of adult male and female rats. Pharmacol Res 2003; 47(1): 75-85.
69. Charlier CJ, Foidart JM: Comparative study of dichlorodiphenyl dichloro ethylene in blood and semen of two young male populations: lack of relationship to infertility, but evidence of high exposure of the mothers. Reprod Toxicol 2005; 20(2): 215-220.
70. Pant N, Kumar R, Mathur N, Srivastava SP, Saxena DK, Gujrati VR: Chlorinated pesticide concentration in semen of fertile and infertile men and correlation with sperm quality. Environ Toxicol Pharmacol 2007; 23(2): 135-139.
71. Iyer P, Makris S: Developmental and reproductive toxicology of pesticides, in: Krienger RI, Hayes WJ. (Eds.) Haye's Handbook of Pesticide Toxicology. third ed Academic Press: California, 2010: 381-440.
72. Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, Mao CS, Redmon JB, Ternand CL, Sullivan S, Teague JL: Study for Future Families Research Team, Decrease in anogenital distance among male infants with prenatal phthalate exposure. Environ Health Perspect 2005; 113(8): 1056–1061.
73. Kluwe WM, Lamb IV JC, Greenwell AE, Harrington FW: 1,2-dibromo-3- chloropropane (DBCP)-induced infertility in male rats mediated by a post-testicular effect. Toxicol Appl Pharmacol 1983; 71(2): 294-298.
74. Sanchez-Pena LC, Reyes BE, López-Carrillo L, Recio R, Morán-Martínez J, Cebrián ME, Quintanilla-Vega B: Organophosphorous pesticides exposure alters sperm chromatin structure in Mexican agricultural workers. Toxicol Appl Pharmacol 2004; 196(1): 108- 113.

75. Lo S, King I, Allera A, Klingmüller D: Effects of various pesticides on human 5α- reductase activity in prostate and LNCaP cells. Toxicol In Vitro 2007; 21(3): 502-508.
76. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C: Male infertility: role of genetic background. Reprod BioMed Online 2007b; 14(6), 734-745.
77. Iammarrone E, Balet R, Lower AM, Gillott C, Grudzinska JG: Male infertility. Best Pract. Res. Clin. Obstet. Gynaecol. 2003; 17(2): 211-229.
78. Krausz C, Corsi PS: Genetic control of spermiogenesis: insights from the CREM gene and implications for human infertility. Reprod. BioMed. Online. 2005; 10(1): 64-71.
79. Gu A, Ji G, Zhou Y, Shi X, Fu G, Wang S, Song L, Wang X: Polymorphisms of nucleotide-excision repair genes may contribute to sperm DNA fragmentation and male infertility. Reprod BioMed Online 2010; 21(5): 602-609.
80. Vani GT, Mukesh N, Prasad BS, Rama Devi P, Hema Prasad M, Usha Rani P, Reddy P: Association of CYP1A1*2A polymorphism with male infertility in Indian population. Clinica Chimica Acta 2009; 410(1-2): 43-47.
81. Aydos SE, Taspinar M, Sunguroglu A, Aydos K: Association of CYP1A1 and glutathione S-transferase polymorphisms with male factor infertility. Fertil Steril 2009; 92(2): 541-547.
82. Safarinejad MR, Shafiei N, Safarinejad S: Assocation of the (TAAAA)n repeat and Asp327Asn polymorphisms in the sex hormone-binding globulin (SHBG) gene with idiopathic male infertility and relation to serum SHBG concentrations. J Steroid Biochem Mol Biol 2011; 123(1-2): 37-45.
83. Merisalu A, Punab M, Altmae S, Haller K, Tiido T, Peters M, Salumets A: The contribution of genetic variations of aryl hydrocarbon receptor pathway genes to male factor infertility. Fertil Steril 2007; 88(4): 854-859.
84. Vicdan A, Vicdan K, Günalp S, Kence A, Akarsu C, Işik AZ, Sözen E: Genetic aspects of human male infertility: the frequency of chromosomal abnormalities and Y chromosome microdeletions in severe male factor infertility. Europ J Obstet Gynecol Reprod Biol 2004; 117(1): 49-54.
85. Thielemans BFJ, Spiessens C, Dhooghe T, Vanderschueren D, Legius E: Genetic abnormalities and male infertility. A comprehensive review. Eur J Obst Gynecol Reprod Biol 1998; 81(2): 217-225.
86. Fox MS, Pera RAR: Male infertility, genetic analysis of the DAZ genes on the human Y chromosome and genetic analysis of DNA repair. Mol Cell Endocrinol 2002; 186(2): 231-239.
87. Safarinejad MR, Shafiei N, Safarinejad S: Association of polymorphisms in the estrogen receptors alpha, and beta (ESR1, ESR2) with the occurrence of male infertility and semen parameters. J Steroid Biochem Mol Biol 2010; 122(4): 193-203.
88. Sermondade N, Elloumi H, Berthaut I, Mathieu E, Delarouzière V, Ravel C, Mandelbaum J: Progressive alcohol-induced sperm alterations leading to spermatogenic arrest, which was reversed after alcohol withdrawal. Reprod BioMed Online 2010; 20(3): 324-327.
89. Said TM, Ranga G, Agarwal A: Relationship between semen quality and tobacco chewing in men undergoing infertility evaluation. Fertil Steril 2005; 84(3): 649-653.
90. Mostafa T: Cigarette smoking and male infertility. JAR 2010; 1(3): 179-186.
91. Bouvet BR, Paparella CV, Feldman RN: Effect of tobacco consumption on the spermatogenesis in males with idiopathic infertility. Arch Esp Urol 2007; 60(3): 273-277.
92. Hassa H, Yildirim A, Can C, Turgut M, Tanir HM, Senses T, Sahin-Mutlu F: Effect of smoking on semen parameters of men attending an infertility clinic. Clin Exp Obstet Gynecol 2006; 33(1): 19–22.
93. Pasqualotto FF, Umezu FM, Salvador M, Borges E, Sobreiro BP, Pasqualotto EB: Effect of cigarette smoking on antioxidant levels and presence of leukocytospermia in infertile men: a prospective study. Fertil Steril 2008; 90(2): 278-283.
94. Viloria T, Meseguer M, Martínez-Conejero JA, O'Connor JE, Remohí J, Pellicer A, Garrido N: Cigarette smoking affects specific sperm oxidative defenses but does not cause oxidative DNA damage in infertile men. Fertil Steril 2010; 94(2): 631-637
95. Gornig VM, Schirren C: Effect of exogenous toxins on fertility. Fortschr Med 1996; 114(14): 169–171.
96. Chia SE, Ong CN, Tsakok FM: Effects of cigarette smoking on human semen quality Arch Androl 1994;33(3): 163–168.
97. Saaranen M, Kantola M, Saarikoshi S, Vanha PT: Human seminal plasma cadmium: comparison with fertility and smoking habits. Andrologia 1989; 21(2): 140–145.
98. Kiziler AR, Aydemir B, Onaran I, Alici B, Ozkara H, Gulyasar T, Akyolcu MC: High levels of cadmium and lead in seminal fluid and blood of smoking men are associated with high oxidative stress and damage in infertile subjects. Biol Trace Elem Res 2007; 120(1-3): 82–91.
99. Wolf R, Shulmam A: Erectile dysfunction and fertility related to cigarette smoking. J Eur Acad Dermatol Venereol 1996; 6(3): 209-216.
100. Sepaniak S, Forges T, Gerard H, Foliguet B, Bene MC, Monnier BP: The influence of cigarette smoking on human sperm quality and DNA fragmentation. Toxicology 2006; 223(1-2): 54-60.
101. Practice committee of American society for reproductive, medicine, Smoking and infertility. Fertil Steril 2008; 90(5): 254–259.
102. Fuetes A, Muñoz A, Barnhart K, Argüello B, Díaz M, Pommer R: Recent cigarette smoking and assisted reproductive technologies outcome. Fertil Steril 2010; 93(1): 89- 95.
103. Freese TE, Miotto K, Reback CJ: The effects and consequences of selected club drugs. J Subst Abuse Treat 2002; 23(2): 151-156.
104. El-Gothamy Z, el-Samahy M. Ultrastructure sperm defects in addicts: Fertil Steril 1992; 57(3): 699-702.
105. Ugboma HAA, Aburoma HL, Ukaigwe P: Adolescent Cannabis Use - a Young Adult and Middle Age Urologic and Reproductive Dilemma: The Niger Delta Malady. Am J Med Med Sci 2012; 2(2): 18-21.
106. Rosen RC: Psychogenic erectile dysfunction Classification and management. Urol Clin Nr Am 2001; 28: 269-278.
107. Whan LB, West MCL, McClure N, and MRCOG Lewis SEM: Effects of delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro. Fertil Steril 2006; 85(3): 653–660.
108. Ragni G, De Lauretis L, Bestetti O, Sghedoni D, Gambaro V: Gonadal function in male heroin and methadone addicts. Int J Androl 1988; 11(2): 93-100.
109. Singer R, Ben-Bassat M, Malik Z, Sagiv M, Ravid A, Shohat B, Livni E, Mamon T, Segenreich E, Servadio C: Oligozoospermia, asthenozoospermia, and sperm abnormalities in ex-addict to heroin, morphine, and hashish. Arch Androl 1986; 16(2): 167-174.
110. George VK, Li H, Teloken C, Grignon DJ, Lawrence WD, Dhabuwala CB: Effects of long-term cocaine exposure on spermatogenesis and fertility in peripubertal male rats. J Urol 1996; 155(1): 327-331.

111. Jia XD, Zhou DX, Song TB: The reproductive system impairment of adult male rats induced by cocaine. Fa Yi Xue Za Zhi 2008; 24(6): 411-413.
112. Li H, Jiang Y, Rajpurkar A, Dunbar JC, Dhabuwala CB: Cocaine induced apoptosis in rat testes. J Urol 1999; 162(1): 213-216.
113. Li H, Dunbar JC, Dhabuwala CB: Role of mitochondrial cytochrome c in cocaine induced apoptosis in rat testes. Urology 2003; 61(3): 646-650.
114. Yang GS, Wang W, Wang YM, Chen ZD, Wang S, Fang JJ: Effect of cocaine on germ cell apoptosis in rats at different ages. Asian J Androl 2006; 8(5): 569-575.
115. Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K: Persistent organochlorines, sedentary occupation, obesity and human male subfertility. Hum Reprod 2005; 20(1): 208–215.
116. Yue D, Yan L, Luo H, Xu X, Jin X: Effect of vitamin E supplementation on semen quality and the testicular cell membranal and mitochondrial antioxidant abilities in Aohan fine-wool sheep. Anim Reprod Sc 2010; 118(2-4): 217-222.
117. Ross C, Morriss A, Khairy M, Khalaf Y, Braude P, Coomarasamy A, El-Toukhy T: A systematic review of the effect of oral antioxidants on male infertility. Reprod Biomed Online 2010; 20(6): 711-723.
118. Lanzafame FM, Vignera SL, Vicari E, Calogero AE: Oxidative stress and medical antioxidant treatment in male infertility. Reprod BioMed Online 2009; 19(5): 638-659.
119. Mendiola J, Torres-Cantero AM, Moreno-Grau JM, Ten J, Roca M, Moreno-Grau S, Bernabeu R: Food intake and its relationship with semen quality: a case-control study. Fertil Steril 2009; 91(3): 812-818.
120. Mínguez-Alarcón L, Mendiola J, López-Espín JJ, Sarabia-Cos L, Vivero-Salmerón G, Vioque J, Navarrete-Muñoz EM, Torres-Cantero AM: Dietary intake of antioxidant nutrients is associated with semen quality in young university students. Hum Reprod 2012; 27(9): 2807-2814.
121. Piomboni P, Gambera L, Serafini F, Campanella G, Morgante G, De Leo V: Sperm quality improvement after natural anti-oxidant treatment of asthenoteratospermic men with leukocytospermia. Asian J Androl 2008; 10: 201–206.
122. Mendiola J, Torres-Cantero AM, Vioque J, Moreno-Grau JM, Ten J, Roca M, Moreno- Grau S, Bernabeu R: A low intake of antioxidant nutrients is associated with poor semen quality in patients attending fertility clinics. Fertil Steril 2010; 93(4): 1128-1133.
123. Cederroth CR, Zimmermann C, Beny LJ, Schaad O, Combepine C, Descombes P, Doerge DR, Pralong FP, Vassalli JD, Nef S: Potential detrimental effects of a phytoestrogen-rich diet on male fertility in mice. Mol Cell Endocrinol 2010; 321(2): 152-160.
124. Lenzi A, Sgro P, Salacone P, Paoli D, Gilio B, Lombardo F, Santulli M, Agarwal A, Gandini L: A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetylcarnitine treatment in men with asthenozoospermia. Fertil Steril 2004; 81: 1578–1584.
125. Bartonelli M, Canale D, Izzo PL, Giorgi PM, Meschini P, Menchini-Fabris GF: L-carnitine and acetylcarnitine in human sperm with normal and reduced motility. Acta Europaea Fertilitatis1987; 18; 29–31.
126. Bornman MS, du Toit D, Otto B, Muller IL, Hurter P, du Plessis DJ: Seminal carnitine, epididymal function and spermatozoal motility. South Afr Med J 1989; 75: 20–21.
127. Ghanayem BI, Bai R, Kissling GE, Travlos G, Hoffler U: Diet induced obesity in male mice is associated with reduced fertility and potentiation of acrylamide-induced reproductive toxicity. Biol Reprod 2010; 82: 96–104.
128. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R: Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility. clinic Fertil Steril 2010; 93(7): 2222-2231.
129. Jensen TK, Andersson AM, Jorgensen N, Andersen AG, Carlsen E, Petersen JH, Skakkebaek NE: Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. Fertil Steril 2004; 82(4): 863–870.
130. Hofny ER, Abdel-Hafez HZ, Kamal ED, Mohamed EE, Abd El-Azeem HG, Mostafa T. Semen parameters and hormonal profile in obese fertile and infertile males. Fertil Steril 2010; 94(2): 581-584.
131. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW: Male obesity and alteration in sperm parameters. Fertil Steril 2008b; 90(6): 2222–2225.
132. Erdemir F, Atilgan D, Markoc F, Boztepe O, Suha-Parlaktas Sahin BS: The effect of diet induced obesity on testicular tissue and serum oxidative stress parameters. Actas Urol Esp 2012; 36(3): 153-159.
133. Wdowiak A, Wdowiak L, Wiktor H: Evaluation of the effect of using mobile phones on male fertility. Ann Agric Environ Med 2007; 14: 169-172.
134. Sheiner EK, Sheiner E, Hammel R, Potashnik G, Carel R: Effect of occupational exposures on male fertility: literature review. Ind Health 2003; 241(2): 55-62.
135. Deepinder F, Makker K, Agarwal A: Cell phones and male infertility: dissecting the relationship. Reprod BioMed Online 2007; 15(3): 266-270.
136. Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J: Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. Fertil Steril 2008; 89(1): 124-128.
137. Kidd SA, Eskenazi B, Wyrobek AJ: Effects of male age on semen quality and fertility: a review of the literature. Fertil Steril 2001; 75(2): 237-248.
138. Colin A, Barroso G, Gomez LN, Duran EH, Oehninger S: The effect of age on the expression of apoptosis biomarkers in human spermatozoa. Fertil Steril 2010; 94(7): 2609-2614.
139. Sarabia FJ, Pizarro DM, Abad MJ, Casanovas IP, Rodriguez-Bertos A, Barger K: Relationships Between Fertility and Some Parameters in Male Broiler Breeders (Body and Testicular Weight, Histology and Immunohistochemistry of Testes, Spermatogenesis and Hormonal Levels). Reprod Domest Anim (In Press) 2012.
140. Sloter E, Nath J, Eskenazi B, Wyrobek AJ: Effects of male age on the frequencies of germinal and heritable chromosomal abnormalities in humans and rodents. Fertil Steril 2004; 81(4): 925-943.
141. Vagnini L, Baruffi RL, Mauri AL, Petersen CG, Massaro FC, Pontes A, Oliveira JB, Franco JG: The effects of male age on sperm DNA damage in an infertile. Reprod BioMed Online 2007; 15(5): 514-519.
142. Desai N, Sharma R, Makker K, Sabanegh E, Agarwal A: Physiologic and pathologic levels of reactive oxygen species in neat semen of infertile men. Fertil Steril 2009; 92(5): 1626- 1631.
143. De Lamirande E, O'Flaherty C: Sperm activation: role of reactive oxygen species and kinases. Biochim Biophys Acta 1784 2008: 106–115.
144. Venkatesh S, Riyaz AM, Shamsi MB, Kumar R, Gupta NP, Mittal S, Malhotra N, Sharma RK, Agarwal A, Dada R: Clinical significance of reactive oxygen species in semen of infertile Indian men. Andrologia 2009; 41: 251–256.
145. Bucak MN, Atessahin A, Yuce A: Effect of antioxidants and oxidative stress parameters on ram semen after the

freeze-thawing process Small Ruminant Research 2008; 75(2-3): 128–134.

146. Hietanen E, Bartsch H, Bereziat JC, Camus AM, McClinton S, Eremin O, Davidson L, Boyle P: Diet and oxidative stress in breast, colon and prostate cancer patients: a casecontrol study. Eur J Clin Nutr 1994; 48: 575–586.
147. Badade ZG, More K, Narshetty J: Oxidative stress adversely affects spermatogenesis in male infertility. Biomed Res 2011; 22(3): 323-328.
148. Tremellen K: Oxidative stress and male infertility—a clinical perspective. Hum Reprod Update 2008; 14: 243-258.
149. Sharma RK, Agarwal A: Role of reactive oxygen species in male infertility. Urology 1996; 48(6): 835–850
150. Kasperczyk A, Kasperczyk S, Horak S, Ostalowska A, Grucka-Mamczar E, Romuk E, Olejek A, Birkner E: Assessment of semen function and lipid peroxidation among lead exposed men. Toxicol Appl Pharmacol 2008; 228: 378–384.
151. Garrido N, Meseguer M, Simon C, Pellicer A, Remohi J: Pro-oxidative and antioxidative imbalance in human semen and its relation with male fertility. Asian J Androl 2004; 6: 59–65.
152. Saleh RA, Agarwal A, Kandirali E, Sharma RK, Thomas AJ, Nada EA, Evenson DP, Alvarez JG: Leukocytospermia is associated with increased reactive oxygen species production by human spermatozoa. Fertil Steril 2002; 78; 1215–1224.
153. Sharma RK, Pasqualotto AE, Nelson DR, Thomas AJ Jr, Agarwal A: Relationship between seminal white blood cell counts and oxidative stress in men treated at an infertility. clinic J Androl 2001; 22: 575–583.
154. Zalata AA, Ahmed AH, Allamaneni SS, Comhaire FH, Agarwal A: Relationship between acrosin activity of human spermatozoa and oxidative stress. Asian J Androl 2004; 6: 313–318.
155. Potts JM, Pasqualotto FF: Seminal oxidative stress in patients with chronic prostatitis. Andrologia 2003; 35: 304–308.
156. Agarwal A, Saleh RA, Bedaiwy MA: Role of reactive oxygen species in the pathophysiology of human reproduction. Fertil Steril 2003; 79: 829–843.
157. Agarwal A, Said TM: Oxidative stress, DNA damage and apoptosis in male infertility: a clinical approach. BJU Int 2005; 95: 503-507.
158. Sikka SC: Role of oxidative stress and antioxidants in andrology and assisted reproductive technology. J Androl 2004; 25: 5–18.
159. Wang X, Sharma RK, Sikka SC, Thomas AJ, Falcone T, Agarwal A: Oxidative stress is associated with increased apoptosis leading to spermatozoa DNA damage in patients with male factor infertility. Fertil Steril 2003; 80: 531–535.
160. Bohring C, Krause E, Habermann B, Krause W: Isolation and identification of sperm membrane antigens recognized by antisperm antibodies and their possible role in immunological infertility disease. Mol Hum Reprod 2001;7: 113-118.
161. Said TM, Paasch U, Glander HJ, Agarwal A: Role of caspases in male infertility. Hum Reprod Update 2004; 10(1): 39-51.
162. Tanaka H, Fujisawa M, Tanaka H, Okada H, Kamidono S: Apoptosis-related proteins in the testes of infertile men with varicocele. BJU Int 2002; 89: 905-909.
163. Tesarik J, Martinez F, Rienzi L, Iacobelli M, Ubaldi F, Mendoza C, Greco E: In vitro effects of FSH and testosterone withdrawal on caspase activation and DNA fragmentation in different cell types of human seminiferous epithelium. Hum Reprod 2002; 17: 1811-1819.
164. Hammoud A, Carrell DT, Gibson M, Sanderson M, Parker-Jones K and Peterson CM: Decreased sperm motility is associated with air pollution in Salt Lake City. Fertil Steril 2010; 93(6): 1875-1879.
165. Meeker JD: Exposure to environmental endocrine disrupting compounds and men's health Maturitas 2010; 66(3): 236-241.
166. Suryavathi V, Sharma S, Sharma S, Saxena P, Pandey S, Grover R, Kumar S, Sharma KP: Acute toxicity of textile dye wastewaters (untreated and treated) of Sanganer on male reproductive systems of albino rats and mice. Reprod Toxicol 2005; 19(4): 547-556.
167. Rana T, Gupta S, Kumar D, Sharma S, Rana M, Rathore VS, Pereira BMJ: Toxic effects of pulp and paper-mill effluents on male reproductive organs and some systemic parameters in rats. Environ Toxicol Pharmacol 2004; 18(1): 1-7.
168. Sokol RZ, Kraft P, Fowler IM, Mamet R, Kim E, Berhane KT: Exposure to environmental ozone alters semen quality. Environ Health Perspect 2006; 114(3): 360-365.
169. Kumar S, Kesari KK, Behari JV: Influence of microwave exposure on fertility of male rats. Fertil Steril 2010; 95(4): 1500-1502.
170. Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, Sharma R: Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an *in vitro* pilot study. Fertil Steril2009; 93(4): 1318-1325.
171. Ray K, Choudhuri R. Effects of radiation on the reproductive system: Reprod Develop Toxicol 2011: 291-299.
172. Pellati D, Mylonakis I, Bertoloni G, Fiore C, Andrisani A, Ambrosini G, Armanini D: Genital tract infections and infertility. Eur J Obstet Gyn R Bio 2008; 140(1): 3-11.
173. Cunningham KA, Beagley KW: Male genital tract chlamydial infection: implications for pathology and infertility. Biol Reprod 2008; 79(2); 180-189.
174. Sergerie M, Mieusset R, Croute F, Daudin M, Bujan L: High risk of temporary alteration of semen parameters after recent acute febrile illness. Fertil Steril 2007; 88(4): 970e1-e7.
175. Bener A, Alansari AA, Zirie M, Alhamaq AOAA: Is male fertility associated with type 2 diabetes mellitus. Int Urol Nephrol 2009; 41(4): 777-784.
176. Hall E, Burt VK: Male fertility: psychiatric considerations. Fertil Steril 2012; 97(2): 434-439.
177. Kelton T: Oxidative stress and male infertility-a clinical perspective. Hum Reprod Update 2008; 14(3): 243–258.
178. Sakata Y, Saegusa H, Zong S, Osanai M, Murakoshi T, Shimizu Y, Noda T, Aso T, Tanabe T: Ca(v)23 (alpha1E) Ca^{2+} channel participates in the control of sperm function FEBS Lett 2002; 516: 229–233.
179. Suarez SS, Ho HC: Hyperactivated motility in sperm. Reprod Domest Anim 2003; 38: 119– 124.
180. Kirkman-Brown JC, Punt EL, Barratt CL, Publicover SJ: Zona pellucida and progesterone-induced Ca2+ signalling and acrosome reaction in human spermatozoa. J Androl 2002; 23: 306–315.
181. Breitbart H: Intracellular calcium regulation in sperm capacitation and acrosomal reaction. Mol Cell Endocrinol 2002; 187: 139–144.
182. Hershlag A, Cooper GW, Benoff S: Pregnancy following discontinuation of a calcium channel blocker in the male partner. Hum Reprod 1995; 10: 599–606.
183. Jequier AM: Male Infertility: A Clinical Guide, second ed Cambridge University Press, New York 2011.

184. D'Cruz SC, Vaithinathan S, Jubendradass R, Mathur PP: Effects of plants and plant products on the testis. Asian J Androl 2010; 12: 468–479.
185. Joshi AR, Ahamed RN, Pathan KM, Manivannan B: Effect of *Azadirachta indica* leaves on testis and its recovery in albino rats. Indian J Exp Biol 1996; 34: 1091–1094.
186. Khillare B, Shrivastav TG: Spermicidal activity of *Azadirachta indica* (neem) leaf extract. Contraception 2003; 68: 225–229.
187. Sathiyaraj K, Sivaraj A, Vinothkumar P, Devi K, Senthilkumar B: Spermicidal activity of *Azadirachta indica* (Neem) aqueous leaf extract on male albino rats. Int J Pharm Tech Res 2010; 2(1): 588-591.
188. Ekaluo UB, Ikpeme EV, Udensi O, Madunagu BE, Markson AA, Omosun G, Umana EJ: Anti-fertility activity of aqueous leaf extract of neem (*Azadirachta indica*) in male albino rats. World J Med Pharm Biol Sci 2011; 1(1): 1-5.
189. Lohiya NK, Manivannan B, Mishra PK, Pathak N, Sriram S, Bhande SS, Panneerdoss S: Chloroform extract of *Carica papaya* seeds induces long-term reversible azoospermia in langur monkey. Asian J Androl 2002; 4(1): 17-26.
190. Verma RJ, Nambiar D, Chinoy NJ: Toxicological effects of *Carica papaya* seed extract on spermatozoa of mice. J Appl Toxicol 2006; 26: 533–535.
191. Naseem MZ, Patil SR, Patil SB: Antispermatogenic and androgenic activities of *Momordica charantia* (Karela) in albino rats. J Ethnopharmacol 1998; 61: 9–16.
192. Yama OE, Duru FI, Oremosu AA, Osinubi AA, Noronha CC, Okanlawon AO: Sperm quotient in Sprague–Dawley rats fed graded doses of seed extract of *Momordica charantia* Middle East. Fertil Soc J 2011; 16: 154–158.
193. Eboetse YO, Ikechukwu DF, Olugbenga OA, Ayodele OA and Caramel NC: Histomorphological alterations in the prostate gland and epithelium of seminiferous tubule of sprague-dawley rats treated with methanolic extract of *Momordica charantia* seeds. Iranian J Med Sci 2011; 36(4): 266-272.
194. Jejeebhoy SJ: Infertility in India - levels, patterns and consequences: priorities for social science research. J Family Welfare 1998; 44(2): 15-24.
195. Anand Kumar TC: *In-vitro* fertilization in India. Curr Sc 2004; 86(2): 254-256.
196. Highland HN, Kalaria B, George LB: A study on the trend in semen parameters of males from Ahmedabad city (Gujrat), over a two-decade period. Ethno Med 2010; 4(3): 199-202.
197. Danadevi K, Rozati R, Reddy PP, and Grover P: Semen quality of Indian welders occupationally exposed to nickel and chromium. Reprod Toxicol 2003; 17(4): 451-456.
198. Kumar S, Sathwara NG, Gautam AK, Agarwal K, Shah B, Kulkarni PK, Patel K, Patel A, Dave LM, Parikh DJ, Saiyed HN: Semen quality of industrial workers occupationally exposed to chromium. J Occup Health 2005; 47(5): 424-430.
199. Adiga SK, Jayaraman V, Kalthur G, Upadhya D, Kumar P: Declining semen quality among south Indian infertile men: Aa retrospective study. J Hum Reprod Sci 2008; 1: 15-18.
200. Mukhopadhyay D, Varghese AC, Pal M, Banerjee SK, Bhattacharyya AK, Sharma RK, Agarwal A: Semen quality and age-specific changes: A study between two decades on 3729 male partners of couples with normal sperm count and attending an andrology laboratory for infertility-related problems in an Indian city. Fertil Steril 2009:1-8.

How to cite this article:
Singh P., Gupta R. , Patidar D. and Singh R.K.: Male Infertility: Causes And Contributors: A Review. *Int J Pharm Sci Res* 2014; 5(6): 2095-12.doi: 10.13040/IJPSR.0975-8232.5(6).2095-12