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Male Infertility; Evidences, Risk Factors, Causes, Diagnosis and Management in Human

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Abstract

Infertility has become ominous problem. On an average, about 10% of all couples face difficulty in starting a family and this creates a feeling of great personal failure, particularly in India where religious and socio-economic traditions have made it almost imperative for everyone to have children. A significant association had been found between impaired semen quality including sperm count, motility and morphology. In this review, the various contributory etiological factors i.e., exposure to heavy metals, pesticides, industrial chemicals, endocrine factors, genetics causes and modern life style had been discussed which have a serious impact on male infertility. In this article we analyzed data from different sources and present evidences of the possible etiology and risk factors for male infertility. There is a need to emerge at the indiscriminate use and disposal of environmental chemicals. Especially pesticides and industrial chemicals as the chemicals enter the food chain, surface and ground water which had potential for exposure during the critical period of development further avoiding tobacco smoking, excessive alcoholism, excessive heat exposure to the testes can help in improving the semen quality.

Keywords: Male infertility; Risk factors; Environmental exposure; Diagnosis

Introduction

The population explosion and infertility are the two major problems of human reproduction. In countries like India, China, Bangladesh, etc., there is an immense increase in population and for this, the agricultural production as well as per capita income has fallen below the requirement. On the other hand, infertility has become ominous problem, which is not just limited to these countries, but is of worldwide incidence. In the UK and USA, it is estimated to be 6% and 10% respectively [1]. In Denmark, it is estimated to be 15.7% [2]. In Nigeria and some parts of sub-Saharan Africa including the Republic of Sudan and Cameroon, infertility rate could exceed 30% [3-5]. Some studies of South-eastern Nigeria, have demonstrated a 65% and 35% prevalent rate for primary and secondary infertility respectively [6]. Similarly, some countries, most notably Kenya, Gabon, Botswana, Zimbabwe and many other African countries, have shown a trend toward lower fertility [4,7-9]. The WHO task force on the diagnosis and treatment of infertility has shown that up to 15% of the population suffers with either primary or secondary infertility [10]. On an average, about 10% of all couples face difficulty in starting a family and this creates a feeling of great personal failure, particularly in India where religious and socio-economic traditions have made it almost imperative for everyone to have children. Another important aspect of this problem in India is that it is the wife alone who has been traditionally blamed for sterility. There are some major causes and risk factors for male infertility i.e., environmental factors, life style factors are discussed in this paper and also thrash out its management

Literature Review

Defining infertility

Infertility is a condition with psychological, economic, medical implications resulting in trauma, stress, particularly in a social set-up like ours, with a strong emphasis on child-bearing. According to the International Committee for Monitoring Assisted Reproductive Technology, World Health Organization (WHO), infertility is a disease of reproductive system defined by failure to achieve the clinical pregnancy after 12 months or more of regular unprotected sexual intercourse [11]. Infertility can be divided into primary infertility and secondary infertility. Primary infertility is the case, when the man has never impregnated a woman. Secondary infertility applies when the man has some time impregnated a woman, even if the women are not the partner in the present couple. The male infertility can be complete or partial termed as subfertility. It possibly due to reduced number of spermatozoa (oligozoospermia), reduced sperm motility (asthenozoospermia), reduced sperm vitality (necrozoospermia), abnormal sperm morphology (teratozoospermia) or any combination of these. Majority of the cases of sub-fertility are caused by an intrinsic testicular disorder.

Standard semen analysis: The important factor

Males were considered infertile with sperm parameters below the WHO normal value [12]. The most significant of these are low sperm concentration (oligospermia), poor sperm motility (asthenospermia), and abnormal sperm morphology (teratospermia). Some other factors are less well associated with infertility include semen volume and other seminal markers of epididymal, prostatic, and seminal vesicle function [13]. The most significant cause of infertility is less sperm concentration, 90% of male infertility problems are related to count and there is a positive association between the abnormal semen parameters and sperm count [14]. The problem with sperm count, motility, and morphology stems from disarray in control mechanism, including pre-testicular, testicular, and post-testicular factors [15].

Hence, semen analysis remains the single most useful and fundamental investigation with a sensitivity of 89.6%, that it is able to detect 9 out of 10 men with a genuine problem of male infertility [16]. Although this assay reveals useful information for the initial evaluation of the infertile male, it is not a test of fertility [17]. It provides no insights into the functional potential of the spermatozoon to undergo subsequent maturation processes required to achieve fertilization [18]. It is a simple test that assesses the formation and maturity of sperm as well as how the sperm interacts in the seminal fluid. It also provides insight not only on sperm production (count), but the sperm quality (motility, morphology) as well [19].

The WHO has revised lower reference limits for semen analyses: The following parameters represent the accepted 5th percentile (lower reference limits and 95% confidence intervals (Cis) in parentheses), derived from a study of over 1900 men whose partners had a time-to-pregnancy of ≤ 12 months [20].

- Volume: 1.5 mL (95% CI: 1.4-1.7)
- Sperm concentration: 15 million spermatozoa/mL (95% CI: 12-16)
- Total sperm number: 39 million spermatozoa per ejaculate (95% CI: 33-46)
- Morphology: 4% normal forms (95% CI: 3-4), using “strict” Tygerberg method [18]
- Vitality: 58% live (95% CI: 55-63)
- Progressive motility: 32% (95% CI: 31-34)
- Total (progressive+nonprogressive motility): 40% (95% CI: 38-42)

Evidences for impaired male reproductive health

In 1992, Carlsen and colleagues first reported a substantial fall in male fertility [21]. They reported that sperm concentration in healthy men appeared to have dropped from 113 million/ml in 1940 to 66 million/ml in 1990 [22]. Carlsen data showed a declination in sperm concentration worldwide i.e., 71.2 million/ml in Ibadan, Nigeria 54.6 million/ml in Lagos, Nigeria, [23] 65.0 million/ml in Salem, Libya, [24] 66.9 million/ml in Dar Es salaam, Tanzania [25] and 57.4 million/ml in Copenhagen, Denmark [26]. A semen sample should ideally contain more than 40 million sperm per ml in order to be considered normal [27]. World Health Organization guidelines suggest that the cut off value for a normal semen sample should be 20 million sperm per ejaculate, with 50% motility and 60% normal morphology. These indicate that if the concentration is less than 20 million sperm per milliliter of ejaculate, fertility may be impaired. In spite of, if the sperm show adequate forward motility concentrations as low as 5 to 10 million can produce a pregnancy [10]. Some andrologists have suggested a lower limit of normal sperm count as 10-15 million per ml [28]. On the contrary, others have suggested 48 million per ml and 55 million per ml, as the lowest values of the normal range for sperm count. Based on data available in the literature on sperm count, only a small proportion of males will have sperm values that satisfy these ideal figures in today's Western industrialized countries. Declination is not limited to sperm count other sperm parameters i.e., sperm motility and sperm with normal morphology also decreasing [26]. According to a Danish study the proportion of abnormal sperm increasing from 40% to 59% between 1966 and 1986 [29]. Furthermore, a study at the Reproduction Biology Laboratory of the University Hospital of Marseille (France) between 1988 and 2007, which included semen analysis of 10,932 male partners of infertile couples concluded that the whole population demonstrated the declining trends in sperm concentration (1.5%/year), total sperm count (1.6%/year), total motility (0.4%/year), rapid motility (5.5%/year), and normal morphology (2.2%/year). Also, in the group of selected samples with total normal sperm count, the same trends of sperm quality deterioration with time were observed [30]. The studies conducted in Indian perspective also showed a qualitative and quantitative defect in the sperm production and declination in sperm count approximately, 30% to 40% men in reproductive age group [31]. Studies conducted in Indian prospective have reported 57% [32] and 19% [33]. Our earlier study conducted for the infertile male of Jaipur, Rajasthan, and study reveals that prevalence of maximum number of infertile males was azoospermic (35%) [34]. The prevalence of azoospermia and oligozoospermia in the metropolitan cities of Mumbai, Bangalore and Jalandhar were similar to those reported in most other parts of the world [35,36]. A study conducted by Mehta et al. [37] had documented that prevalence’s of azoospermia in Kurnool and Jodhpur, respectively, was 38.2% and 37.3% incidences of azoospermia. In this respect the presence of azoospermia in Jaipur was within range, as reported in Indian perspectives, but higher than those reported from other part of the world [32,33,38-41].

Causes and Risk Factors of Infertility

The major causes of infertility identified to be testicular failure, obstruction, cryptorchidism, low semen volume, sperm agglutination, idiopathic infertility, varicocele, erectile or ejaculatory dysfunction, abnormal viscosity, endocrine disorder, high density of sperm, congenital abnormalities and environmental causes [42]. According to Sherins, 50% cases of male infertility are idiopathic [43]. Broadly the caused factors

for male infertility can be divided into non-genetic and genetic factors. Among the non-genetic factors previous exposure to disease which influences the fertility either directly or indirectly. Diabetes is associated with increased sperm nuclear and mtDNA damage that may impair the reproductive capability of these men [44]. Testicular function is temperature dependent and requires a temperature 2°C to 4°C below body temperature [45]. Fever exceeding 38°C can also affect the spermatogenesis for the succeeding six months.

Molecular insight into male infertility

Genetic causes: The genetic basis of infertility has received increasing recognition in recent years. Several kinds of chromosomal abnormalities are associated with infertility: deletion, inversion, mutation, aneuploidy, and translocation. Of these, translocation is most common chromosomal abnormality. A study showed that the frequency of chromosomal translocations was 2.1% in infertile men [46]. Chromosomal translocations can be of many types- Robertsonian translocation, reciprocal translocation and these account for 10% of the causes of male infertility [47]. Robertsonian translocations are defined as translocations involving acrocentric chromosomes [13-15,21,22]. Carriers of Robertsonian translocations are phenotypically normal; however, they exhibit reproductive dysfunction, such as oligospermia in males [48]. It is now obvious that genetic etiology for infertility is an important cause of disrupted spermatogenesis. Genetic damage in sperm can occur at several levels, all of which have the potential to cause infertility in men. Sperm DNA is known to contribute one half of the genomic material to offspring. Thus, normal sperm genetic material is required for fertilization, embryo and fetal development and post-natal child wellbeing [49]. Various *in vivo* and *in vitro* studies have suggested that disturbances in the genomic organization in sperm nuclei are negatively correlated with the fertility potential of spermatozoa [50]. Investigations have also shown that these disorders play an important role in failure of intracytoplasmic sperm injection (ICSI) and intrauterine insemination (IUI). In males the prevalence of genetic factors seems to be inversely related to the sperm count. Our earlier study was also documents a negative correlation between DNA damaged cells and sperm motility [34]. There is a concern that these genetic abnormalities can be transmitted to the male progeny, who may subsequently have a more severe phenotype of infertility. The incidence of chromosome factors in infertile males ranges between 2 and 8% increased to 15% in azoospermic males in recent years [51-54]. FSH is an important hormone which is required for initiation of spermatogenesis is requisite to monitor in infertile men from the point of therapeutics and clinical intervention. Normal FSH is indicative of germinal epithelial destruction, but elevated FSH is associated with both normal as well as aberrant spermatogenesis, where testicular histology could show Sertoli cell only (SCO) syndrome, Hypo-spermatogenesis is seen where the quantity of spermatogenesis is decreased and is known to be associated with either normal or elevated FSH [55]. The rate of carry home alive and healthy birth is low especially when DNA damaged sperm is used in ART. Recurrent ART failure cause financial, emotional and psychological stress on the couples.

Advancement in molecular biology enabled the identification and characterization of underlying genetic causes of male infertility. Genetic causes must be sought by systematic evaluation of infertile men and affected couples informed about the implications of such diagnoses for assisted reproductive technology outcome and their potential offspring. An association between human male infertility and chromosomal anomalies has been known for a long time [56,57]. The incidence of karyotype abnormalities among patients with infertility has been reported to range between 2% to 21%, being low among azoospermic men [58-60].

The possible association between chromosomal abnormalities and male infertility became evident following the result of the first large karyotype survey involving subfertile males [56,61]. The Y chromosome in mammals carries the gene that switches the development of the indifferent gonad from the default female pathway to the male pathway and results in the development of the testis [62]. Long ago macroscopic deletions in the long arm of Y chromosome were suggested to be responsible for azoospermia [63]. With the advancement in molecular biology, three non-overlapping regions, to as azoospermia factor (AZF a, b and c from proximal to distal Yq) have been defined as spermatogenesis loci [64].

The AZF microdeletions are the prevalent cause of male factor infertility. Germ cell development is under the control of a large number of genes on autosomes and on the Y chromosome. The long arm of the Y chromosome contains genes and gene families involved in spermatogenesis and are critical for germ cell development and differentiation. In 1992, Vollrath [65] and colleagues constructed a 43 interval deletion map of a human Y chromosome that contained on ordered array of sequence tagged sites (STS) that spanned the entire length of the Y chromosome. The genes critical for spermatogenesis are located on the long arm of the Y chromosome in deletion interval 5 and 6 bend 11.23. This region is referred to as the AZF as the most severe phenotype associated with its deletion is azoospermia. The AZFa locus is located on proximal Yq11 (Yq 11.21), while AZFb and AZFc are located on distal Yq 11 (Yq 11.23). Deletion of these loci results in spermatogenic arrest and is associated with azoospermia, oligozoospermia and also with a varied testis histological profile ranging from Sertoli cell only (SCO) to hypo-spermatogenesis to maturation arrest. The average Y chromosome microdeletions for infertile males were 8.2% and majority of deletions (84.3%) were associated with azoospermia [66]. These deletions in fertile controls have been reported to be less than 1% and no deletion has been detected in men with normal semen analysis [67]. The genetic basis of infertility is very complex and is determined by many factors. These factors influence the development of gametes, the reproductive organs both external and internal, their physiology and the development of embryo and its further differentiation. Genetic disorders can be chromosomal, single gene mutations or can be multifactorial. Extensive research

has been conducted for having a better insight into the genetic basis of infertility [68].

Genetic counseling educates the patients about the genetic make-up and any risk that may be conferred to progeny. It gives them reproductive choice also. A significant proportion of couples in reproductive age suffer from primary and secondary infertility. Although, varieties of possible causes on male infertility, as mentioned above, have been identified in majority of cases, the diagnosis of male infertility revolves around the routine semen analysis. Documented database is scary in our country that covers data on all aspects of male infertility and there is an urgent need for the same to identify the underlying causes of infertility with preventive strategies.

Environmental factors

Humans are exposed to numerous exogenous as well as environmental chemicals through various routes. During the past 50 years, the rapid expansion of chemical industries in both the developed and developing countries has resulted in release of a plethora of xenobiotics into the environment. Male reproductive system is highly sensitive to these environmental factors that lead to infertility [69]. These alien molecules, including pesticides, herbicides, cosmetics, preservatives, cleaning materials, municipal and private wastes, pharmaceuticals and industrial by-products enter our bodies in a variety of forms. Exposure to chemical contaminants, which are estrogen mimics and endocrine disruptors, has been implicated as one of the possible factors contributing to the increasing male infertility.

Heavy metals: Human being could be exposed to heavy metals at trace concentrations usually through intake of contaminated water and food or contact with contaminated air or soil. Heavy metals including lead (Pb), cadmium (Cd), mercury (Hg) could adversely affect the male reproductive system, either by causing hypothalamic c-pituitary axis disruption or by directly affecting spermatogenesis, resulting in impair semen quality. A tendency towards reduced semen quality has been recorded in men exposed to heavy metals [70-72]. Sallmen et al. [73] found that lead exposure induce childless rather than delayed pregnancy. Increased risk of spontaneous abortion was found in cases of pregnancies in which the father worked as a stainless steel welder, whereas pregnancies in which the father was a welder of other metals was not at any increased risk [69]. There is considerable agreement that high or even moderate concentrations of lead cause fertility problems in humans. Fatima et al. [74] showed that >40 µg/dL of lead in blood cause a decline in sperm count. In addition, they observed lower motility (<50%) and morphology (<14%), with >35 µg/dL in whole blood. Telisman and colleagues also showed that high lead concentration in blood significantly lowers sperm density and motility (36.7 µg/dL) [75]. High concentrations of lead seem to be clearly associated with sperm damage. At high concentrations, cadmium could also affect semen quality. According to Akinloye et al. men with high concentrations of cadmium in seminal plasma (65 µg/dL) had less sperm count and 36% of motile sperms [76]. There is clear evidence that increased concentrations of mercury in the body will be harmful for sperm. Choy et al. showed that high concentrations of total mercury (inorganic and organic) measured in whole blood (40.6 mmol/L) resulted in <50% of progressive motility, <14% of normal morphology, and of sperm concentration [77]. However, in a study of Lidia et al. suggests that there is no correlation between the concentrations of any of the metals in the three biological samples analyzed (whole blood, blood plasma, and seminal plasma) [78].

Pesticides and other polychlorinated hydrocarbons: Exposure to pesticides affects many body organs including reproductive system. Spermatogenesis, testis weight and sperm parameters such as, sperm density and motility, sperm counts, viability, inducing sperm DNA damage, abnormal sperm morphology affected by organophosphoruses. It affects the male reproductive system by mechanisms to reduce the weight of testes, epididymis, seminal vesicle, and ventral prostate, seminiferous tubule degeneration and changes in hormone levels of testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) and also affects the antioxidant enzymes in testes, and inhibited testicular steroidogenesis are other possible mechanisms [79].

Men working in the agriculture sector are at more than ten-fold increased risk of infertility in comparison to those in other occupations [80]. Exposure of the father to pesticides during the preconception period or prior can also increase the risk of having anencephalic child [81]. Men engaged in agricultural practices adopting use of pesticides are at increased risk of fetal death from congenital anomalies, particularly where pesticides are used massively [82]. Paternal pesticide exposure has been otherwise reported to decrease fertilizing ability of sperm in those seeking IVF treatment [83]. Pre-conceptional paternal pesticide exposure is reportedly associated with an increased risk of acute lymphoblastic leukemia in children aged 0.9 years [84]. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is one of the most toxic man-made chemicals. A study conducted by Mocarelli et al. (2000) [85] reveals that a population exposed to TCDD was linked with lowered male to female sex ratio in offspring whose parental exposure was through paternal route rather than maternal.

Free radicals

Oxidative stress (OS) plays an important role in human reproduction. It arises as a consequence of excessive ROS production and/or impaired antioxidant defense mechanisms [86]. Owing to their deleterious effects on human spermatozoa, excessive ROS must be continuously inactivated to keep only a small amount necessary to maintain normal cell function [87]. Oxidative stress-mediated damage to the sperm plasma membrane may account for defective sperm function observed in a high proportion of infertile patients [88].

The most common ROS that have potential significance in reproductive biology, include the superoxide anion (O2-), hydrogen peroxide (H_2O_2), the peroxyl (ROO-) and the hydroxyl (OH-) radicals [89,90]. Reactive oxygen species (ROS) has both physiological and pathological roles in male infertility. The physiological level of ROS plays a crucial role in processes such

as maturation, capacitation, acrosomal reactions, and fertilization [91,92]. On the other hand, pathological levels of ROS, which can originate from endogenous sources such as leukocytes [93,94] and immature/abnormal spermatozoa [95,96]. Oxidative stress is not routinely checked in andrology lab, because of its cost and complexity of testing and the lack of a single standardized measure of oxidative stress. The assessment of quality of sperm DNA has become essential with the increase in the use of assisted reproductive techniques (ART) in infertility managment. *In vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) techniques bypass several natural selection barriers that are present throughout the male and female reproductive tracts until the sperm enters the oocyte [97]. Investigations have shown disorder results into failure of ICSI and intrauterine insemination (IUI) and one of the main causes of defective offsprings [98]. The rate of live birth is low especially when sperm with DNA damage is used in ART. The H_2O_2 caused a dose-dependent deleterious effect on sperm DNA integrity and sperm function in both fertile and infertile group, however, in infertile group effect was more severe. Our previous study shows that DNA integrity of spermatozoa harshly deteriorate at 300 µM of H_2O_2 within 10 min of incubation period when incubated *in vitro* though, sperm motility, vitality and other sperm functions did not affected at this level [99].

Life style

Lifestyle factors are amendable habits and ways of life that can greatly influence overall health and wellbeing, including fertility. Advancing paternal age, occupation has been implicated in a broad range of abnormal reproductive and genetic outcomes. Lifestyle factors, including age when starting a family, nutrition, weight management, exercise, psychological stress, cigarette smoking, recreational and prescription drugs use, alcohol and caffeine consumption, may impact fertility [100].

Age: Understanding the effect of male age on fertility has also become important in public health because of a great number of men are choosing to father a child at older age. Advanced age has negative impact basal membrane, seminiferous tubules and tunica albuginea of testis. The Leydig cells decrease in number and accumulate the “ageing” pigment lipofuscin [101,102]. Age causes localized changes in spermatogenesis, which include a reduction in dark type and intratubular clustering of pale type spermatogonia. A Spermatogenesis arrested at the spermatocyte I stage and numerous malformation in spermatids have been noticed [103]. A study conducted by Sharma, also documents that age is intimately related to decreasing sperm motility and vitality, whereas, least effect is observed on sperm count. Normal sperm parameters were observed at age ≥ 20-30 years while the most significant reduction in sperm parameters occurred after the age of 35 years [104].

Obesity: Obesity is a worldwide problem and levels are intensifying all over the world. To classify the overweight and obesity in adult population and individuals, body mass index (BMI) is a simple index of the weight-to-height ratio. Infertility is more prevalent among men with elevated BMIs. Excess weight is not only linked to increased risk of chronic disease [105], but also increases the risk of reproductive problems [106]. Considering the patho-physiology of obesity it has negative impact on male fertility [107]. Jensen et al. [108] studied over 1558 younger men having paramilitary physical and found that overweight men had reduced sperm concentration as compared with normal weight. The effect of BMI on sperm parameters has been apparently investigated in several scientific studies which document that prevalence of azoospermia or oligozoospermia were associated with an increased overweight and obesity [109]. Our previous investigation about BMI and sperm function also clarify that sperm function with sperm concentration, motility and vitality shows a significant and negative relationship with body mass index (BMI); In contradictory to Thomsen et al. [110] investigation, our results shows a significant declination in sperm concentration, motility and vitality in overweight and obese male as compared to normal male. However, sperm morphology is least affected with elevated BMI [111]. Underweight men also showed markedly decreased sperm function as compared to normal weight subjects. Our results are in accordance with Kort et al. study [112] which shows a negative relationship and declination in motility and vitality in per BMI group as compared to normal BMI group.

Smoking: Tobacco smoke is deleterious to reproduction. Benzo[a]pyrene (B[a]P) is a potent carcinogen in cigarette smoke. Its reactive metabolite adducts with DNA, which can result in mutations [113]. This can result in both male and female infertility. Women who smoke, reportedly, have lower estrogen and progesterone levels, poor LH surge (causing irregular menses and ovulation), longer time to conceive, increased risk of miscarriage, bleeding during pregnancy, babies of low birth weight during IVF and earlier menopause. Male smokers have been shown to have decreased sperm counts, impaired sperm motility, more abnormal sperm and reduced testosterone levels; they can potentially contribute to congenital abnormalities and asthma in their children. Heavy paternal smoking may increase the risk of childhood cancer in the offspring [114]. According to a report, heavy smokers had 19% lower sperm counts than non-smokers [115]. Ji et al. [116] found that the more a man smokes prior to his wife’s conception, greater will be the risk the child will have for developing cancer by the age of five years. It has been indicated that exposure of spermatozoa from non-smokers to the seminal plasma of smokers yields a significant reduction in the sperm motility, acrosome reaction and elevated MDA [117]. Waylen et al. [118] provided in their meta-analysis evidences for a negative effect of smoking on clinical outcomes of intracytoplasmic sperm injection success (clinical pregnancy) in women with smoking and non-smoking partners (22% vs. 38%). However, Rybar et al. [119] failed to confirm a relationship between smoking and sperm quality in men from any of the investigated groups.

Consumption of alcohol: Alcohol use in males can affect spermatogenesis and/or sperm physiology and may even cause impotence. It is reported that 75% of children with fetal

alcohol syndrome have fathers who were alcoholics [120]. Alcohol consumption is associated with a deterioration of sperm parameters which may be partially reversible upon alcohol consumption discontinuation [121]. Although, paternal alcohol consumption has been shown to affect the growth and behavior of the offspring, the mechanisms underlying these effects still remain to be elucidated. Alcohol-induced reduction in cytosine methyltransferase mRNA levels may reflect altered genomic imprinting caused by reduced DNA methylation, which in turn may lead to the expression of normally silent paternal alleles [122].

Recreational drugs: Cocaine exposure of males before the wife conceives is linked to abnormal development in the offspring, since cocaine can bind with high affinity to human spermatozoa. Therefore, sperm may act as a vector of cocaine transport to the ovum [123]. Use of methamphetamine, cocaine and marijuana is associated with increased risk of a variety of birth defects affecting specific organ systems [124]. Merijuana, containing the chemical 9-tetrahydrocannabinol (THC), may be directly toxic to the egg. The THC is structurally similar to testosterone and binds to the receptors to which testosterone should bind. A cardiac birth defect is attributable to paternal use of marijuana [125]. Monosodium glutamate (MSG), a common flavor-enhancer added to foods like accent, flavored potato chips, Doritos, cheetos, meat seasonings and many packaged soup was found to cause infertility in test animals. In a study Pizzi et al. had showed that male rats fed MSG before mating had less than 50% success rate (5 of 13 animals), whereas those not fed MSG had over 92% success rate (12 of 13 animals). Also, the offspring of the MSG-treated males had shorter body length, reduced testes weights and evidence of overweight at 25 days of MSG treatment [126].

Use of mobile phone: Concerns about the possible health effects of mobile phone usage are growing as the number of users has increased tremendously over the past several years. Mobile phone technology uses radiofrequency electromagnetic radiation (RF-EMR) and has drastically increased the RF-EMR exposure encountered in daily life. Increased risk of stillbirth with increasing preconceptional exposure to ionizing radiation was reported for fathers working at the Sellafield nuclear site in Cambria, UK [127]. Leydig cells, seminiferous tubules, and spermatozoa are the main targets of the damage caused by mobile phones on the male reproductive tract. In particular, cellular phone exposure reduces testosterone biosynthesis, impairs spermatogenesis, and damages sperm DNA. Scrotal hyperthermia and oxidative stress are the main mechanisms by which the damage is generated [128]. A Study conducted by Gorpinchenko et al. (2014) showed a positive correlation between mobile phone radiation exposure, DNA-fragmentation level and decreased sperm motility [129]. However, reports showed a statistical insignificance effect on sperm quality parameters according to cell phone use, but there were statistical differences in the frequencies of sperm concentration, volume, viscosity, liquefaction time and means of immotile sperms and abnormal morphology [130]. From this point of view, the habit of keeping a mobile phone in the trouser pocket or the duration of its use may have an impact on possible generation of hyperthermia and oxidative stress as well. Radiation may harm sperm by damaging DNA, disrupting Leydig cells or causing shrinkage of the seminiferous tubules. Where men use their mobile phones for more than four hours a day, 40% drop in sperm motility and viability was reported [131].

Diagnosis and Management for Infertility

Taking adequate medical history and physical examination of both couple is crucial step in infertility workup. During investigating the causes of male infertility, history of occupational or therapeutic exposures to radiations, childhood infections in the form of mumps, undescended testes, chronic illnesses (like diabetes, thyroid disease, hypertension, tuberculosis, mumps or other venereal infections), testicular injuries (occupational, trauma), previous sexually transmitted diseases which may block the ducts, genetic absence of vas deferens, and varicocele should be obtained. Immunological tests will also be done to determine the presence of antisperm antibodies in the blood and semen. Detection of herpes simplex virus (HSV) in the semen of infertile men using polymerase chain reaction (PCR) techniques is fundamental pace in diagnosis of infertility.

Testicular deficiency may have different aetiologies and present clinically as severe oligoasthenozoospermic (OAT) or non-obstructive azoospermia (NOA) [120]. In men with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia: when spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are within the normal range. However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status because men with maturation arrest histology could have normal FSH and normal testis volume and still be azoospermic [12,132]. Testicular biopsy can be part of intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA. Testicular sperm extraction (TESE) is the technique of choice. Spermatogenesis may be focal, which means that in about 50% of men with NOA, spermatozoa can be found and used for ICSI.

The investigation of infertile male patients is essential in order to identify potentially treatable causes of infertility and to guide therapy. There are several treatment possibilities for management of male infertility. Some strategies suggested or proposed for avoiding male infertility include the following: Antioxidant therapy to reduce the excess ROS and the patient should be immediately advised to avoid tobacco use as abstinence from tobacco use could help lower seminal ROS levels. Lifestyle modifications such as losing weight for obese men, eating of fruits and vegetables are also helpful. There is also an urgent needs to look at the indiscriminate use and disposal of environmental chemicals especially pesticides,

industrial chemicals as the chemicals enter the food chains and surface and ground water and could be potential for exposure during the critical period of development. Our knowledge of the molecular genetics of human fertility is expanding rapidly. It is now possible to detect the incidence of chromosomal abnormalities using a variety of highpowered polymerase chain reaction (PCR) techniques and multicolour fluorescent *in situ* hybridization (FISH) analysis Before patients can be subjected to ICSI, FISH-sperm studies are necessary to understand whether there is a genetic cause for male infertility.

Discussion

Regardless of their contributions in prokaryotic evolution, still little is revealed due to lack of extensive correspondences between them with the exception for DNA sequences involved in duplication and recombination which obscure phylogenetic analyses based on gene descent and synteny [21,22]. In order to solve this problem to some extend Blast2 network, a bioinformatics approach is used to provide an immediate conception of the similarities, existing among DNA and protein sequences based on similarity networks rebuilding and phylogenetic profiling. This will in turn, opens the possibility to trace the evolutionary aspects and origin of the entire plasmids and not only of single genes and/or operons harbored by them [23].

Conclusion

Thus, the above-mentioned segregation mechanisms of plasmid ensure maintenance of plasmid copy number to normal levels and their inheritance to the bacterial progeny.

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