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# Causes Of Male Infertility

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***Abstract***

Infertility has been the major concern faced by 10–15% of the married couples, in spite of trying for conception for almost 1 year. There are several reasons for the cause of infertility in males and females. This review article mainly includes the discussions on various idiopathic factors directly or indirectly affecting the fertility of men, though both males & females are affected by the same. Idiopathic Male Infertility (IMI) means an abnormality in seminal parameters due to an unknown cause. When the hormones and the testis microenvironment are disrupted due to idiopathic factors or any other factors, the seminal characteristics are affected, which will lead to infertility.



**KEY WORDS:** Male Infertility, Idiopathic factors, Sperm parameters, Smoking, Alcohol, Drugs, Obesity

## INTRODUCTION

Infertility could be either male infertility, female infertility, combined infertility, or unknown reasons. In such cases, if the normal medication or ovulation induction does not work, then a physician or a gynaecologist may advise the couples to undergo in vitro fertilization (IVF). Several factors affect both males and female leading to infertility. The most common factors that cause infertility in females are ovulatory disorders, endometriosis, pelvic adhesions, tubal blockage, other tubal/uterine abnormalities, and hyperprolactinemia (50). Likewise in males, there are certain factors causing infertility, such as testicular dysfunction, endocrinopathies (51), and abnormal seminal parameters. Both male & female fertility is basically affected by one common reason: lifestyle.

Without any particular reason, 30% of men show poor sperm quality (decrease in count, motility, viability & morphology), which is known as idiopathic male infertility. Some studies suggest that men with idiopathic infertility may have undisclosed morbid disease due to exposure to pollution and reactive oxygen species, by which the immunological microenvironment of the testis may be disrupted, leading to poor sperm characteristics in-depth, resulting in sperm DNA damage, and finally, when normal genetic/epigenetic functions are interrupted, males would lose overall fertility potential (52).

Although it is well known that smoking is injurious to health and affects the male reproductive system, smoking prevails all over the world. Nowadays, females also prefer smoking in spite of knowing the negative effects on overall health. It is concerning that the alcohol consumption habit is implicating people from the age of 12 years, especially in countries like the United States. A survey conducted by the European Commission says that 76% of European citizens are consuming alcoholic beverages in a year (5). The use of marijuana has increased in many countries, particularly among youngsters. They are unaware that they may have a negative effect on health, including fertility or reproductive function. This active compound of marijuana is Δ9-tetrahydrocannabinol, which will bind to the related cannabinoid receptor. The presence of cannabinoid

receptors in human testicles indirectly affects the spermatogenetic process (12). Male infertility is affected by various factors, but lifestyle and the kind of food intake play a crucial role, and if followed in a proper way, improvements can be seen in fertility outcomes and sperm quality (14). The real problem started when the western diet practice spread all over the world. Since then, the infertility issues are on the rise, and with males, the seminal quality has deteriorated (22).

**CAUSES**

There are multiple causes which contribute to the male infertility. It can be divided into Congenital, Acquired and idiopathic.

**Table:1- Multiple causes contributing to male infertility (1)**

| S.NO | Congenital factors | Causes | Acquired factors | Causes |
|---|---|---|---|---|
| 1. | Anorchia *Congenital Anorchia (rare -1:20,000) *Acquired Anorchia - | torsion, trauma, infection, failed surgery, or castration | Varicocele | Venous drainage of the developing testis. More prominent during puberty (41). |
| 2. | Congenital absence of vas deferens *Bilateral *Unilateral | Genetic | Testicular trauma | Testicular injuries |
| 3. | Cryptorchidism | Genetic | Testicular torsion | Decrease in blood flow to the testis |
| 4. | Y chromosome microdeletions | Genetic defect | Germ cell tumours | somatic driver mutations |
| 5. | Chromosomal or genetic abnormalities | Genetic | Acquired hypo - gonadotrophic hypogonadism | abnormal decrease in the capacity of the gonads to function (42) |
| 6. | Klinefelter syndrome and its variants (47, XXY; 46, XY/47, XXY mosaicism) | Genetically Developmental delay | Recurrent urogenital infections (prostatitis, prostatevesciculitism) | chronic bacterial prostatitis (43) |
| 7. | Kallmann syndrome | delayed sexual development (44) | Post inflammatory conditions | epididymitis, mumps orchitis |
| 8. | Robertsonian translocation | Chromosomal abnormality (45) | Urogenital tract obstruction | Sexually transmitted infections (STIs) & Uropathogens (46) |
| 9. | Mild androgen insensitivity syndrome | X-linked genetic disease (47) | Exogenous factors (e.g., chemotherapy, medications, radiation, heat) | |
| 10. | Genetic endocrinopathy | Hormonal Imbalance (48) | Systemic diseases (live cirrhosis, renal failure | |
| 11. | Congenital obstruction | Atresia or stenosis, Midline Prostatic cystic lesions (49) | Anti-sperm antibodies | The blood–testis barrier |

**IDIOPATHIC RISK FACTORS:**

**SMOKING:**

Many studies have reported that the smoking habit negatively affects sperm parameter which results in male infertility. Total sperm count, motile sperm, morphology was significantly reduced in smokers (2). A cigarette lit consists of 4000 compounds which include vaporized liquids and particles through various process. Cigarette consumption effect is related with the number of cigarettes used per day. According to a study, usage of 20

cigarettes per day increases the level of cadmium (6,7). While another study says that the cadmium levels in the seminal fluid is directly correlating with the number of cigarettes consumed per day (8).
Another study examined the correlation between the semen parameters and the seminal zinc. The study concluded that the level of seminal zinc is lower in smoker when compared to nonsmoker which is also associated with low sperm concentration, decreased motility and morphology (3). Wong WY. et. al, conducted a study on 210 men. The study was based on analysing the level of cotinine concentration of cotinine, the greater were the abnormal sperm morphology. Since cotinine is a metabolite of nicotine, the abnormal sperm morphology would be the possible effect of smoking habit (4). A large cohort study of 1786 men including 655 smokers and 1131 nonsmokers showed that there was a decrease in sperm concentration, total sperm counts and the motility in smokers when compared with nonsmokers. Also, there was a slight reduction in the ejaculate volume and the normal forms of sperm(morphology) in smokers but not in a significant degree (2)

**ALCOHOL:**

**Table 2: Various studies on alcohol consumption**

| S.NO | SAMPLE SIZE | ALCOHOL | PERIOD | RESULT |
|---|---|---|---|---|
| 1. | 685 | Yes | 30-60 minutes (Daily) | Delayed liquefaction of Seminal Fluid, Low sperm motility (7) |
| 2. | 3000 | Yes | Daily | Urethritis (8) |
| 3. | | Yes | Daily | Increased Leukocyte Concentration (9) |
| 4. | 20 | Yes (Alcohol Dependence Syndrome) | Daily | Decrease in Seminal Fluid volume, Sperm concentration, Abnormal sperm morphology (10) |
| 5. | 66 | Yes | Daily 180ml per day for 5 days per week for ≥1 year | Decrease in Volume, Count, Motility, Percentage of morphology (11) |
| 6. | 1221 | Habitual Alcohol intake | Consuming more than 5 units/day in the recent 30 days (Binge drinking). | Decrease in sperm concentration, total count, normal morphology (58) |

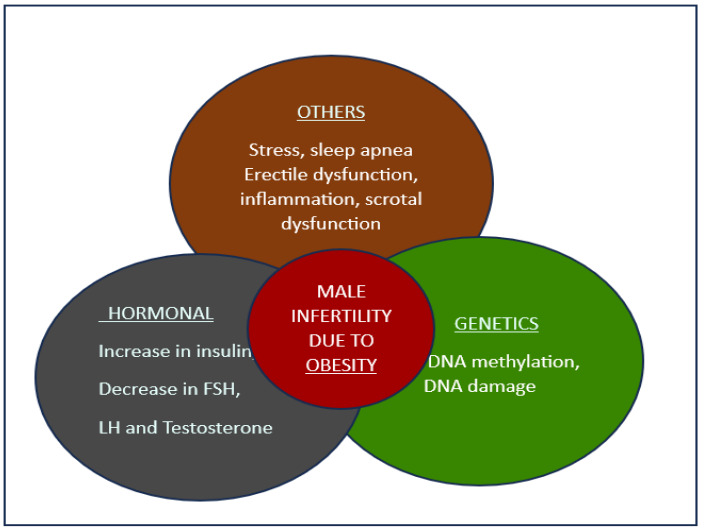
Research was done to find out the association of alcohol intake and semen parameters in men with primary and secondary infertility. For this study 776 infertile men from China were included and grouped based on the alcohol intake. According to the study, men grouped as secondary infertility group with moderate and heavy alcohol consumption resulted in smaller testis volumes and lower sperm concentrations. The study was concluded that there is a higher chance of affecting men with secondary infertility who has a habit of heavy alcohol consumption. The seminal parameters of men with primary infertility are affected by alcohol consumption (6). A study reported that the fertilization failure & risk of reduced live birth rate is associated with the alcohol consumption (57). But another study evaluated that the consumption of alcohol is not associated with the oxidative DNA damage in sperm in terms of 7-hydro-8-oxo-20-deoxygenosis(8-oxodG) (59).

**RECREATIONAL DRUGS:**

A recent retrospective cross-sectional study showed that there is direct toxic effect on spermatogenesis through the oxidative mechanism (13), where regular cannabis users where selected to assess the chromosomal abnormalities using fluorescence in-situ hybridization and deoxynucleotidyl- transferase- mediated (Dutp) nick end labelling method were used to know the level of DNA fragmentation. By this study it is concluded that the chromosome abnormalities, rates of sperm aneuploidy, diploidy and DNA fragmentation were significantly higher in cannabis users when compared with control. Prescribing opiates/opioids has been increasing and it is a concerning challenge health wise worldwide (15). The opioid molecule affects the male spermatogenesis by suppressing the androgen hormone. It also suppresses the hypothalamic dopamine secretion, which will in turn reduces the inhibitory impact of the dopamine on the release of prolactin from anterior pituitary gland. While some studies show no significant impact on the level of prolactin & gonadotropin although tested with low level of testosterone.
But another study revealed that when opioid administration is stopped, the androgen levels were back to normal similar to the level prior to prescription (16). Amphetamine- Type Stimulants (ATS) & Novel Psycho-active Substance (NPS), Herbal high & Psychedelics are other 2 types of recreational drugs but comparing ATS, NPS has very less or no effect on male infertility (17).

**OBESITY:**

**Fig 1: Obesity factors affecting Male fertility (21)**



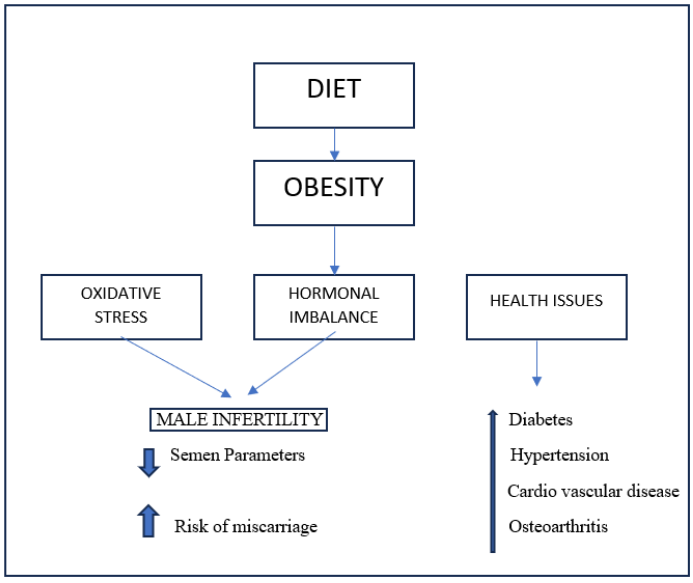

A major concern for both men and women are obesity across the world. Obesity and adiposity are particularly affecting the adult population. This is mainly because of reduced physical activity and increased junk food intake. If the body mass index (BMI) is more than 30 kg/m2 then it is called as obesity. It results in diabetes, hypertension, stroke, chronic illness, premature aging (18). In male the obesity or waist expansion affects the semen parameters like concentration and reduces the chances of achieving live birth after undergoing infertility treatment (19).

Likewise in female obesity adversely affects the menstrual cycle, process of ovulation and fertility (20). In addition, both male and female obesity may increase the risk of reduced chance of success rate and live birth rate. Most of the body functions or mechanisms will be related to the physical factors, genetics, immune system and endocrine modulation. These may be altered/disturbed by obesity which affects the process of spermatogenesis, sperm DNA integrity, sperm functions & the total sperm quality resulting in male infertility (21)

**DIETARY FACTORS:**

Numerous factors like lifestyle, physical activity, drugs affect human health including infertility. Diet plays a very important role in maintain overall mechanism of the body. Mona S Almujaydil says that dietary nutrients have great effect on male reproductive potential. Especially omega- 3 fatty acids, vitamins, minerals & other phytochemicals play a very important role in sperm parameters & functionality in male infertility.

**Fig 2**: Negative effects of improper diet (23)

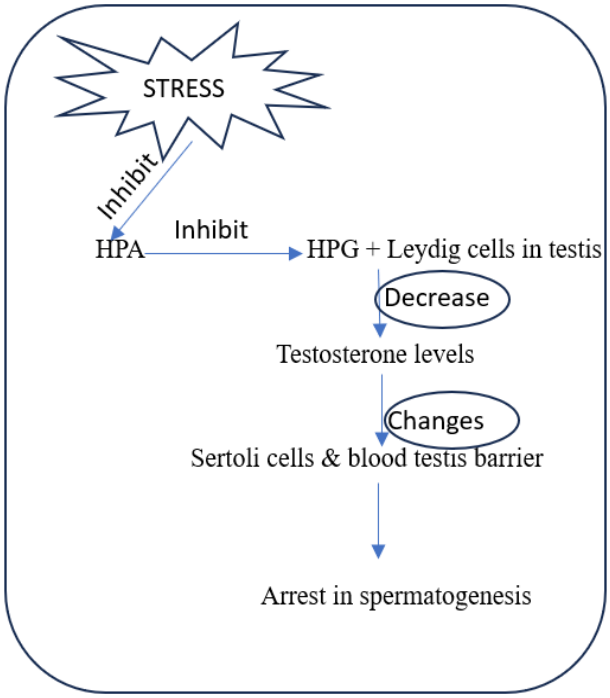


Most of the research in which qualitative analysis is done, the diets rich in omega-3 fatty acids, antioxidants such as Vitamin E, Vitamin C, β- carotene, selenium, zinc, cryptoxanthin & lycopene. Other vitamins which include vitamin D, folate has a positive impact on quality parameters (23). Foods which are high in calories with hyperglycaemic index & high fatty foods with low fibre index leads to obesity which means excessive body weight resulting in the development of diseases namely sleep apnoea, hypertension, diabetes, osteoarthritis & cardiovascular disease (24, 25). Studies shows that polyunsaturated fatty acids (PUFA) play a very important role in mitochondrial energetic metabolism & also helps in reducing oxidative damage. Because fatty acids act as the energetic metabolism & also helps in reducing oxidative damage. Also, fatty acids which can be derived from the dietary sources act as the energy suppliers for the gamete membrane (60)

**PSYCHOLOGICAL STRESS:**

There are limited studies on the effect of psychological stress on humans. But there are many studies on animals suggesting that the psychological stress has an adverse effect on spermatogenesis. This is occurred mainly due to the variation in the secretion of hormone called testosterone (26)

**Fig 3: Path of stress leading to the arrest of Spermatogenesis (26).**




**NOTE: HPA- Hypothalamic pituitary adrenal axis, HPG – Hypothalamic pituitary gonadal axis.**

The couples who undergo infertility treatment often has psychological stress. The effect of psychological stress in an individual varies according to the emotional strength, situation & also due to some religious beliefs. Hence there are different dimensions in different individuals affecting their reproductive health (27). Especially male experiences erectile problem due to severe psychological stress. This stress is usually due to the pressure from the society and family. Sheikh et al says that "any factor which alters the health of an individual negatively has ad adverse effect on the functions of the body" (29).

**ADVANCED PATERNAL AGE:**

Researchers focused on only Advanced Maternal Age (AMA) which may be the direct cause of anomalies in foetus, miscarriage, growth restriction, preterm delivery. Very few studies are there explaining the effect of Advanced Paternal Age (APA) and the direct mechanism on how it declines the male fertility. APA has adverse effects on sperm production due to the increasing Follicle- Stimulating hormone (FSH) & decreasing testosterone serum levels. The seminal volume, motility & morphology decreases with the increase in paternal age. Many studies have shown that the APA has lower probability of pregnancy either through Intra Cytoplasmic Sperm Injection (ICSI) and naturally. While few studies have not shown the same result (30). Hence lower pregnancy rate & higher miscarriage rate is associated with APA, independent of maternal age.

There is a direct correlation between paternal age & decreases sperm quality and testicular function (53). A study conducted by Mahmoud et al conclude that men above 75 years of age has 31 % of testicular volume which is less when compared with the men aged 18 – 40 years. As men gets older the blood flow to the testis is reduced (54). Hence this insufficient blood flow to testis will lead to hernia like protrusions, reduced spermatogenesis & a thicker basement membrane. The Sertoli cells & the seminiferous tubules play a major role during spermatogenesis. Hence, as men gets older the Sertoli cells count is dropped & their endocrine & paracrine functions which provides nutrients & structural support is also reduced or stopped (55). So, beyond the age of 35, slowly the sperm parameters especially motility, vitality and normal morphology starts declining & after 45 the semen production is reduced with less sperm count and viability (56).

**ENVIRONMENTAL OR OCCUPATIONAL EXPOSURE TO TOXINS:**

**Table 3: Effects of major chemicals on male infertility (32)**

| S.NO | CHEMICALS | USAGE | EFFECT |
|---|---|---|---|
| 1. | Endocrine Disrupting Chemical | Food & Industrial Solvents | Affects Reproductive health (33) |
| 2. | Polychlorinated Biphenyl | Industrial products | Direct effect on Spermatogenesis (34) |
| 3. | Bisphenol A | Baby Bottles, plastic, Containers | Disrupts Androgen receptors, Spermatogenesis failure (35) |
| 4. | Phthalate | Colour, Scent, Cosmetics | Anti Androgenic,<br>Decreased sperm motility,<br>Increase Sperm DNA damage (36,37) |
| 5. | Pesticides & Herbicides | Agriculture | Affects Reproductive health & functions (32) |
| 6. | Organophosphate | Pest Control at home, Agriculture (39) | Decreases Sperm count, motility, viability.<br>Increases abnormal sperm morphology and sperm DNA damage (38) |
| 7. | Dichlorodiphenyl-Dichloroethylene | Malaria vector control | Inhibition of Spermatogenesis,<br>Reduction of testis weights<br>Reduction in Sperm counts, motility, viability, increasing abnormal morphology and DNA damage of sperm (38) |

Wijesekara, G.U.S et al analysed the level of lead (Pb) & cadmium (Cd) in seminal plasma to understand whether the environmental occupational exposure has any effect on the seminal parameters of men. The result showed that 54.6% were exposed to environmental or occupational toxins out of which 38.3% of men affected with lead & 23% of men were detected with cadmium. Hence decreased sperm count, motility & morphology is associated with the exposure of environmental or occupational toxins (31). Exposure to chemicals used in industries & in agriculture as fertilizers and pesticides can affect the reproductive hormones & lead to infertility (32). A systematic review & meta-analysis explained that there is a decline in sperm count, concentration, total motility, normal sperm morphology in 349 male subjects who were exposed to organophosphate (OP) compared to 417 male subjects who were unexposed controls (40)

**CONCLUSIONS:**

All the couples trying for conception should consider to reduce the risk of idiopathic factors like Smoking, Alcohol, Recreational drugs, Obesity, Psychological stress, Advanced paternal age, Dietary factors, Environmental or occupational exposure to toxins. Although there are no particular treatments or medication available to completely cure the age-related infertility, making changes in lifestyle and including antioxidant supplementation may help minimize the effects on male fertility especially improvement in spermatogenesis & decrease the rate of sperm DNA fragmentation. More research had to be done in-depth on how the idiopathic factors affect the fertility of male.

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