

# Male Infertility Risk Factors and Potential Causes: A Scoping Review

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**Abstract**— Despite research indicating that sperm counts are decreasing globally and that male infertility is becoming more common, limited studies have been conducted on the probable causes and risk factors for male infertility. Because there are few primary treatments for male unproductiveness, knowing the reason and risk characteristics will help identify particular ways to prevent it.

**Keywords**— male infertility, risk factors, causes, scoping review

## I. INTRODUCTION

Abnormalities in spermatozoa caused by insufficient numbers (azoospermia /oligosperma) , poor motility and aberrant structure / morphology have been described as the main causes of male infertility globally [1, 2]. In fact, throughout the past few decades, systematic decreases in sperm counts have been observed in a number of studies [3,4], a circumstance that reflects the male factor's increasing contribution to the rise in the incidence fertility problems worldwide [5]. The World Health Organization (WHO) has reported that there has been a decline in quality and quantity of spermatozoa, it led to the revision of the standards for determining whether sperm counts are normal or abnormal to be utilized by andrology laboratories around the world. [6].

Additionally, it has been stated that male infertility is a type of fertility issues that does not improve to initial treatment. According to reports, only a small portion of male factor infertility can be treated successfully using traditional methods [7]. By contrast, the majority of secondary treatments for male factor infertility include "intra-cytoplasmic sperm transfer [8], in vitro fertilization and embryo transfer [9], intra – uterine insemination [10] , artificial insemination [11] and child fostering / adoption"[12].

Limited studies have been conducted on the probable causes and risk factors for male infertility, despite the condition's rising prevalence and difficult treatments. Recognizing the main causes and prognostic factor will make it possible to identify primary prevention strategies as well as efficient primary treatment strategies for male infertility. A better knowledge could encourage the development of creative secondary and tertiary solutions to the issue. In

the literature, a variety of potential reasons and risk factors for male infertility have been speculated or documented. Among these include: "smoking, drinking, using drugs, being overweight, having had or currently having testicular infections, being exposed to environmental pollutants, being exposed to extreme heat, hormonal issues, ejaculatory/erectile abnormalities and testicular injuries [13].

Nevertheless, to date, there hasn't been much data of investigations that analyze and assess these prospective causes and risk factors in ways that would allow for the identification of straightforward preventive and therapeutic approaches as well as the establishment of understanding regarding the mechanism causing male infertility [11].

There are two goals for the study:1) to find review that have been published on the risk and causes for male infertility in addition to determine the most common reasons recorded globally 2) to detect gaps of possible risks and reasons affecting on male, providing further focused investigation and development.

## II. RISK FACTORS AND CAUSES FOR MALE INFERTILITY

The causes and risk factors of male infertility as identified in the reviewed studies are presented using three broad themes : "behavioral/ life style risk factors , Environmental exposure and biological / physiological causes " .

### A. Behavioral / lifestyle risk factors

- Age

Many men are choosing to have children later in life, so it is crucial for public health to understand how male age affects fertility. Most men decrease blood testosterone with age, "even men who are healthy and this loss likely started at age of thirty" [14]. After age 30, testosterone levels begin to diminish by about 1% annually, which is known as the andropause [15]. However, "symptomatic hypogonadism in aging males" would be a more technically correct term to describe the decline in testosterone. Because the level of testosterone that causes dysfunction varies greatly among individuals, "hypogonadism is not defined by any specific level of serum androgens" [16]. Symptomatic hypogonadism in elderly men is associated with a variety of symptoms,



including "decreased libido, decreased muscles mass, decreased bone mineral density, increased fat mass, central obesity, insulin resistance, emotional irritability, dysphoria and erectile dysfunction" [17]. Sharma's research further shows that sperm motility and vitality are directly correlated with age-related declines, although sperm count is least affected. Normal sperm parameters were seen between the ages of 20 and 30 years, however after the age of 35, sperm parameters began to significantly decline [18]. Similarly, Pasqualotto et al., [17] reported males over thirty-five years old have a doubled possibility of being infertile compared to males under twenty-five years old, and it takes them five times as long to get pregnant at 45 years old. A study comparing a control group of men under the age of (52 years) to 55 health men ranging in age (from 52-79 yrs) revealed that "older men had lower semen volume, aberrant sperm morphology and decreased vitality" [19]. According to a study conducted in Belgium by Mahmoud et al., "the volume of a man's testicles in his eighth decade was 31% lower than that of the younger control group, who were between at ages 18-40 years old" [20].

- Smoking, Alcohol Intake, Medication

Garba-Alkali et al. studied into the statistical correlation between semen analysis and particular variables. [21]. The examination of the semen "both normal and abnormal" was statistically associated with the following male infertility risk factors: history of sexual transmits disease (STD) treatment, cigarette smoking, and alcohol consumption. Increased levels of abnormal sperm than normal semen were found in all categories except for alcohol consumption, and there was a strong correlation between "risk factors and semen analysis".

The toxins found in cigarette smoke (Benzo[a]pyrene (BaP) is deleterious and impaired reproduction [22, 23]. Elbardisi et al. [24] in a recent investigation suggest that "smoking can be one of the factors responsible for sperm DNA fragmentation" thus diminished motility, motility, decrease sperm count, more abnormal sperm and reduced testosterone levels. Additionally, "smoking has been linked to an increase in the levels of ROS that cause oxidative stress in the environment". This oxidative stress may be harmful to sperm and cause oxidative damage because it may exceed seminal plasma's antioxidant capacity [25]. Smoking was also linked to a higher incidence of erectile dysfunction [26]. Additionally, heavy parental smoking may raise the risk of children developing cancer [27]. According to a seminal fluid analysis report by Meri et al. [28] for 1438 men, smoking has a significant impact on sperm motility.

Amongst smokers, "heavy smokers 20 or more cigarettes per day had lower sperm concentration and a higher proportion of aberrant sperms than non-heavy smokers". In contrast, sperm motility and morphology were not significantly affected by smoking duration in an Iranian study; even so, increase of one cigarette daily resulted in a 1% reduction in sperm motility [29].

Alcohol consumption behaviors are significantly influenced by social and cultural factors. Religious and sociocultural values in Arabic-Islamic communities have a detrimental impact on alcohol intake as compared to other western societies [30]. Alcohol consumption in men has a negative impact spermatogenesis and/or sperm physiology in which "reduced gonadotropin release, testicular atrophy,

decreased testosterone and sperm production" and may even cause impotence and affect fertility [31, 32]. According to Condorelli et al., [33], heavy drinkers have been demonstrated to have lower semen quality indices and even azoospermia. Okonofua et al. [34] showed a correlation between alcohol consumption and male infertility. "1-2 glasses of alcohol per day and weekly" compared to occasional alcohol intake. In addition to that, according to Bielawski et al., [35], seventy-five percent of fetuses with fetal alcohol syndrome have alcoholic fathers.

Various medications was also found to effect on infertility through influence on a direct toxic effect on the gonads or the hypothalamic-pituitary-gonadal axis such as "Glucocortico-steriod, antineoplastic agents cyclophosphamide, methotrexate, busulphan and chlorambucil, antibiotics cotrimoxazole and sulfasalazine, hormonal steroids estrogen, medroxyprogesterone acetate, the constituents of oral contraceptives and diethylstilbestrol, neuroplastic agents, cimetidine, spironolactone, opiates, marijuana, thyroid supplements, and colchicine" [36].

- Body Mass Index (BMI)

Numerous studies have linked abnormal BMI, which can be low or high, to an increased risk of male infertility [37]. A "low sperm count and poor spermatozoa motility were associated with abnormal BMI low or high", While males with normal BMI (20-24 Kg/m<sup>2</sup>) had the highest mean sperm count and motility (39.35 million/mL) [38]. Male infertility and body mass index are significantly positively correlated, while progesterone (ng/mL) and oestradiol are strongly correlated with BMI, sperm count decreases as body mass increases [39]. Among sperm parameters, sperm concentration was the only one that was significantly decreased in males with "high BMI compared to those with normal BMI" according to Alshahrani et al., [40]. However, sperm morphology is least impacted by an increased BMI. [41]. According to a review, the main factor reducing the fecundity of obese men is a hormonal deficiency called hypotestosteronaemia, and the causes of infertility in these men can be treated [42]. Obese infertile males have shown inflammatory and obstructive epididymitis pathology in addition to abnormal semen quality. [42] Interestingly, infertility may also be inherited to the offspring through the sperm if conception happens as a result of obesity-related epigenetic changes in the sperm that reduce fertility. [43].

### B. Other Behavioral/lifestyle risk factors

- Environmental exposure

Numerous exogenous and environmental substances are exposed to humans through a variety of mechanisms. An abundance of xenobiotics "have been released into the environment over the past 50 years" due to the chemical industries' rapid development in both developed and industrialized nations. The environmental variables that cause infertility are highly sensitive to the male reproductive system [44]. "Pesticides, industrial chemicals, preservatives, cleaning products, municipal and private waste, pharmaceuticals, industrial by products, and mycotoxins" are just a few of the foreign substances that "enter our bodies in various ways and have the ability to act either directly as

spermatotoxins or via a steroidal pathway" [4]. According to a study carried out in Lebanon, exposure to physical and chemical substances such (pesticides, cement at work , solvents and gasoline) increased the chance of male infertility, although metal pollution had little of an impact. [45]. Additional investigation in Saudi Arabian found that male infertility was more common among bakers who were exposed to high temperatures at work [46].

By disrupting the gonadal endocrine system or by having a direct detrimental effect on spermatogenesis, air pollution may be a factor in men's reproductive health issues [47]. The Middle East and North Africa (MENA) region has high energy and carbon concentrations from an environmental aspect. In comparison to non-MENA regions, the MENA region had higher CO<sub>2</sub> emissions, according to a recent analysis published in 2013[48]. Due to this region's population's high exposure to environmental toxins and the global warming effect's rising temperatures, the male reproductive system is significantly impacted [49].

Comparing men in other occupations with men in the agricultural sector, there is a more than tenfold increase in the risk of infertility [50]. Pesticide use at work resulted in male infertility and dysfunctional testicular [51]. Its impact on the testicular antioxidant enzymes, testosterone levels , luteinizing hormone (LH), follicle-stimulating hormone (FSH) and seminiferous tubule degeneration as well as other potential mechanisms include inhibited testicular steroidogenesis [52], also diminish sperm's ability to fertilize in people undergoing IVF [53]. "Children at age nine-years old are more likely to be born have increased risk of acute lymphoblastic leukemia and anencephalic children" if the father was exposed to pesticides before or during the preconception period [54, 55]. Studies by Oliva et al., [56] in Argentina included (225male), have shown "a strong correlation between exposure to solvents and pesticides with poor sperm count". Additionally, compared to men who weren't exposed to pesticides, exposed men had higher serum oestradiol concentrations, while males had lower LH concentrations when exposed to solvents than males who unexposed. According to Aneck-Hahn et al., [57] a study of 311 young males on seminal parameters in Limpopo South Africa, indoor Dichlorodiphenyltrichloroethane (DDT) spraying has a negative impact on male infertility.

Humans may be exposed to heavy metals at very low levels by consuming contaminated food and water, or by getting into interaction through polluted soil or air. Lead (Pb), cadmium (Cd), copper (Cu), and mercury (Hg) are heavy metals that can disrupt the male reproductive system by altering spermatogenesis or the hypothalamic-pituitary axis then impairs the quality of the semen and leads to infertility [58]. According to Fatima et al., [59], blood lead concentrations greater than 40 µg/dL reduce sperm counts. They also noticed reduced motility (50%) and morphology (14%), with whole blood having >35 µg/dL. Another case-control research conducted in Nigeria by Akinloye et al. [60] found a significant association between male infertility and exposure to Cd toxicity (65 g/dL). "High levels of total mercury (inorganic and organic) measured in whole blood (40.6 mmol/L) were shown by Choy et al.,[61] to produce less than 14% of normal morphology, 50% of sperm concentration, and of progressive motility" There is a link between aflatoxin and male infertility. In a case –control study, spermatozoal anomalies were more prevalent in

infertile men with aflotoxin in their semen than in fertile men. [62].

- Electronic devices

Long-term use of a laptop will raise the scrotal temperature and negatively affect sperm parameters [63]. Furthermore, Over the past several years, there has been a significant increase in the number of mobile phone users, because "radiofrequency electromagnetic radiation (RF-EMR) that is produced by mobile phone technology and significantly increased the amount of RF-EMR in people are exposed every day then has a negative impact on male fertility" since it results in lower-quality semen [64]. For dads who worked at the Sellafield nuclear station in Cambria, UK, there was a correlation between increased pre-conceptual exposure to ionizing radiation and an increased chance of stillbirth [65]. The main targets of the damage caused by mobile phones on the male reproductive tract include "Seminiferous tubules, Leydig cells, and spermatozoa".According to a study by Gorpichenko et al., [66], exposure to mobile phone radiation is positively correlated with higher levels of DNA fragmentation and reduced sperm motility. Another study found a correlation between the amounts of time spent using a cell phone and the actual proportion of live sperm [67]. There has been a 40% decline in sperm motility and viability when men use their phones for longer than four hours each day [68].According to this theory, using a phone for a prolonged period of time or keeping one in one's trouser pocket may have an impact on the induction of oxidative stress and hyperthermia.

### III. BIOLOGICAL/ PHYSIOLOGICAL CAUSES

According to the study, "the major biological or physiological causes triggering male infertility were oligozoospermia, asthenozoospermia, azoospermia, or a combination of these". 1737 participants were divided into three groups for a nine-year prospective research conducted in Estonia.Absolute (genetic disorders, obstruction of seminal tract, secondary hypo-gonadism.), severe (severe sexual dysfunction, oncological diseases,) and plausible (urogenital tract congenital abnormalities, secondary or acquired testicular injury) [3].

- Genetic and chromosomal disorders

Chromosome abnormalities, micro-deletions in the Y chromosome and single gene mutations are among the genetic reasons of severe male infertility, which account for 10-15% of cases [69]. Various levels of male subfertility or infertility may result from a genetic disorder that affects spermatogenesis, interferes with the genital tract's normal development, reduces sperm motility, and impairs fertilization potential [70]. It is well known that sperm DNA provides 50% of the genetic material for offspring. The development of the embryo, fetus, and post-natal child all depend on normal sperm genetic material [71]. Earlier research also shows a negative relationship between sperm motility and DNA-damaged cells [18]. There is a worry that these inherited disorders could pass to the male offspring, who might then have an even more severe form of infertility.

"Genes and gene families involved in spermatogenesis and essential for the growth and differentiation of germ cells are found on the long arm of the Y chromosome". A long time ago, it was thought that oligozoospermia, azoospermia, and a variety of testicular histopathological disorders, such as

hypospermatogenesis, Sertoli cells alone (SCO), and maturation arrest was caused by deletion in the long arm of Y chromosome [72]. "Three non-overlapping areas known as azoospermia factor (AZF a, b, and c from proximal to distal Yq) have been recognized as the spermatogenesis locus as a result of discoveries in molecular biology" [73]. These deletions were recorded to be not more than 1% in fertile controls, and no deletion was found in men with normal semen analysis [74]. Other most common of chromosomal abnormality is translocation, the frequency of chromosome translocations were seen in 2.1% of infertile men. There are numerous types of chromosomal translocations: these include reciprocal translocation, Robertsonian translocation, and 10% of male infertility's (oligospermia) causes can be attributed to them [75].

Glutathione S-transferase Mu-1 gene polymorphism (GSTM1) was examined in a case-control study of a sample of Egyptian males with unexplained infertility., "a higher frequency of the GSTM1 null genotype was found significantly lower sperm concentration and sperm count in infertile men compared with GSTM1-positive genotype in fertile men" [76]. In order to evaluate the various forms of chromodomain protein, Y-linked 1 (CDY1) gene deletions, their impact on male infertility and spermatogenesis in Tunisia, 241 infertile and 115 fertile men participated in a case-control research, compared to men who were fertile, deletion of the CDY1b were significantly more common in infertile males. [77]. "Methylene tetrahydrofolate reductase (MTHFR) and cystathionine beta- synthase (CBS) genes have both been shown to have many mutations", leading to extremely hyperhomocysteinemia (HHcys) [78]. A relationship between HHcys and altered spermatogenesis has been documented recorded [79]. A risk factor for endothelial dysfunction is HHcys. Due to the penis' high degree of vascularization, erectile dysfunction (ED) can be classified as primarily a vascular disorder. It has been proposed that HHcys may increase the risk of vasculogenic ED as a result. [80]. One in six infertile males in this line has ED. [81]. Because the genetic causes of infertility are so complicated, much study has been done to gain a better understanding of these causes.

- Male reproductive tract infection

"An infection of the male reproductive system is believed to be one of the potentially curable reasons of male infertility", which constitutes more than 1 million cases every day worldwide, while it's a common condition that can reduce the quality of spermatozoa and disrupt the function of the male accessory gland. "Zinc levels, semen volume,  $\alpha$ -glucosidase and fructose levels" in seminal plasma are all significantly lower in male reproductive tract infections, indicating a possible impairment of the epididymis secretory function, seminal vesicles and prostate [82]. A recent study in Iran by Ahmadi et al., [83] revealed that "11% *Neisseria gonorrhoeae* and *Chlamydia trachomatis* 12.5% were the two most prevalent bacterial species found in the semen of infertile men and associated with sperm abnormality and decreased fertility". Infertile men were substantially more likely to have bacterial organisms in semen culture according to a case-control study in Southern Nigeria, such as "*Trichomonas vaginalis*, *Staphylococcus aureus*, *Candida albicans* and *Streptococcus faecalis*" and correlated with physiologically and biologically "poorer sperm motility and lower sperm concentration <5 million" than fertile men" ;

The study also revealed that men's infertility was linked to past genital ulcers, painful micturition, and penile discharge [34].

- Varicocele

"Testicular veins within the pampiniform plexus of the spermatic cord, which supports a man's testicles, "dilation" in a condition known varicocele. The most common treatable reason for infertility in males who visit an infertility clinic for examination is varicoceles. [84]. According to Cozzolin and Lipshultz [84], adults and adolescents with varicocele account for 15% of the overall population, although male patients at infertility clinics seem to have varicocele at a rate of 30 to 40% [85]. "In 2016, Jeje et al. reviewed 70 cases of male infertility in Lagos, Nigeria, [86], In 53 of the 70 cases, varicocele was found; 24.3% of them had a unilateral varicocele, while 51.4% had a bilateral varicocele, unilateral varicocele occurred only in 30 cases (42.9%), it happened in conjunction with hormonal imbalance in 22 cases, and vas occlusion in 1.4%.

- Free radicals

One of the main risk factors for male infertility is high DNA fragmentation in spermatozoa, which is mostly induced by "oxidative stress" (OS) [87]. It results from an excessive accumulation of "reactive oxygen species" (ROS) and /or compromised antioxidant defense mechanisms [88]. Excessive ROS must be constantly neutralized to maintain only the minimum quantity for the proper cell function [89]. It is believed that many cases of idiopathic oligospermia are caused by "free radical or oxidative damage to sperm". Males are significantly more likely to develop aberrant sperm and sperm counts when exposed to higher levels of free radical sources [36]. According to perior study, which found that the DNA integrity of spermatozoa begins to rapidly decrease within 10 minutes of incubation in vitro at 300  $\mu$ M of H<sub>2</sub>O<sub>2</sub> however, sperm motility, vitality and other sperm activities were unaffected at this level [90].

- Endocrinal disorders

Male infertility due to endocrine factors is frequently referred to as having pre-testicular etiology. In these cases, either a hormone deficiency or an excess leads to the impairment of fertility [9], about 15% of married couples experience hormonal disturbance, with men accounting for about 50% of those issues. The hypothalamus, pituitary, and testes must all function normally for a man to become fertile, and the development of the entire male germ cell depends on the glands' balanced endocrine production. [92]. Male infertility may be caused by abnormalities in the production of hormones. Hypo-gonadotrophic hypo-gonadism" is usually present, with inability of pituitary glands to produce enough" follicle stimulating hormone and luteinizing hormone" thus result lower sperm count and infertility [93]. Given that spermatogenesis occurs in close proximity to Sertoli cells, thyroid hormones must have a crucial regulatory function in the production of sperm. Consequently, alteration in function of thyroid may have an impact on spermatogenesis and male fertility [94]. There is a significant prevalence of hypothyroidism, with a range of 6.18% to 47.34%, based on a comprehensive assessment of thyroid problems within Arab world in 2016 [95]. Long-term thyroid deficiency during puberty or childhood can also cause "delayed ejaculation, erectile dysfunction, decreased libido and reduction in quality of semen". In this regard, it is

advised that people with ED and aberrant sperm, the thyroid hormone levels recommended. [96]. Additionally, by causing "hypogonadism and hyperandrogenism", hyperglycemia and insulin insufficiency might decrease fertility [97]. Pre-testicular, testicular, and Post-testicular pathogenic mechanisms have been proposed. Not only is glucose metabolism an important process not only necessary for sperm cell motility following epididymal maturation but also during spermatogenesis. Additionally, "mature sperm require glucose to have the ability to fertilize".

#### IV. CONCLUSION

The prevalence of infertility has significant effects on demographic and health in the world, and over the last thirty years as regards male factor infertility accounts for 40% of infertility cases which increased as a problem. The aim of the investigation was to establish and offer new research the plausible "male infertility causes and risk factors" based on existing data.

Ageing was the risk factor mentioned in the research under review that was highlighted the most frequently. In this study, male infertility behavioral risk factors included alcohol consumption, smoking, high body mass index, and medication use. These risk variables were described in case-control or cross-sectional studies, which indicate a lack of evidence for causation. Nutritional counseling may also improve reproductive outcomes. To demonstrate causation and identify potential mechanisms of action, more extensive research is needed.

Exposure to chemicals, different pesticides, heavy metals, air pollution and mycotoxins were the main environmental risk factors and influences "both reproductive health and overall health" that this review identified, there is a need for authorities and the general population to become more aware of environmental protection issues. It is crucial to perform more systematic study to confirm potential causes of infertility because the usage of these chemicals for agricultural and home purposes is increasing in many nations.

According to cell phone use, this review showed a statistical significance in "the frequencies of volume, sperm concentration, immotile sperm count, viscosity, abnormal morphology and liquefaction time". Radiation can effect on sperm by "Leydig cells disrupting, DNA damage, or contracting the seminiferous tubules".

In addition to uro-genital infections and varicocele, this review also explored genetic variables that have been implicated in human spermatogenesis to date. Despite the fact that the significance of chromosomal abnormalities including deletions and translocations chromosomes has long been recognized, around 13% of people with human azoospermia have "a microdeletion in the AZF region of Y chromosome". New human azoospermia culprit genes are predicted to be found in regions other than the Y chromosome in an even lower proportion 7%, according to recent reports.

In order to decrease the prevalence of pelvic inflammatory illness and subsequent infertility due to (STDs), "C.trachomatis and N. gonorrhoeae" screening and treatment efforts should be implemented. In this regard, male sexual health and STD prevention programs can undoubtedly enhance reproductive health.

Varicocele has reportedly been linked to infertility over the years. However, this finding has been contradicted by numerous other studies. Though, "varicocelectomy remains controversial as a treatment for male infertility". The effectiveness of varicocelectomy and the precise role of varicocele in the causation of male infertility must therefore be established in a randomized control trial or meta-analysis.

On sperm parameters, reactive oxygen species have a detrimental impact. "An imbalance between the antioxidant system and ROS formation is indicated by high ROS levels in the semen". Damage from an elevated ROS level can result in cell death or sperm dysfunction. Many cases of idiopathic oligospermia are thought to be caused by free radical or oxidative damage to sperm.

The information gaps that must be addressed in order to have a complete understanding of the real causes of male infertility have been identified". In our opinion, enhance comprehension of the "causes of male infertility" will make it easier to develop primary preventive and to guide therapy for male infertility.

#### ACKNOWLEDGMENT

We would like to thank all of the investigators who participated in the reflection's writing our manuscript.

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