Understanding Male Infertility: A Comprehensive Review of Causes, Etiology, Epidemiology, and Risk Factors

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Abstract

Infertility is a condition of the male or female reproductive system that is defined by the inability to become pregnant following more than 12 months of unprotected, common, or sexual behaviour. Numerous studies have shown that around thirty per cent of occurrences of infertility are due to males alone. Along with this, one of the most difficult situations a man may experience is receiving a diagnosis of male infertility. It can be disastrous for some people. The main goal of infertility in male evaluation is the identification of contributing causes, treatment that are reversible and assisted reproductive procedures (ART) and counselling for all the issues that are irreversible as well as untreatable. Additionally, Male infertility occasionally may be a sign of a more serious ailment that further causes life threatening problems or disorders. Hence, this is yet another justification for thorough evaluation of the male members of infertile couples, helps to detect and treat any serious underlying medical issues. Also, this review helps to understand and aims to provide a comprehensive overview of male infertility and their Causes, aetiology, Diagnosis, Epidemiology, Risk Factors, or management of men with infertility with current controversies and future endeavours.

Keywords: *Male Infertility, Sperm Selection, Infertility, Evacuation issue, Ovulation, Infertile couples.*

1. INTRODUCTION

Male Infertility

Infertility is a disorder itself rather than a symptom of disease that is defined as the disease of reproductive system in which couples is unable to have children [1]. It can either affect men as well as women or both. Generally, this is not a life-threatening disorder, but it is still considered as a very stressful life experience for couples due to infertility and they may get depressive episodes because of this [2]. This disease can be curable but in very rare cases this problem or disease cannot be treated. Male partner or female partner or both partners may have infertility concerns if a man and a female engage in recurrent unprotected sex for more than a year and the female does not become pregnant, it can be considered as the primary or first sign of infertility [3].

Additionally, male infertility is the problem of reproductive system that stops couples from impregnating female. There can be numerous causes of this disorder but one of the major causes include lower sperm production, abnormal sperm or the blockage which prevent the delivery of sperm or any kind illnesses that harm reproductive system, any past or current injuries, some chronic health problems, bad lifestyle choices and many other factors as well that may contribute to male infertility [4]. There are various causes of male subfertility which can be related to congenital, acquired, idiopathic factors that impair spermatogenesis [5]. Additionally, Male fertility may be impacted by a variety of elements including both curable and irreversible illnesses [6]. Age differences between the couples, medication or steroid usage, history of recent or prior surgery, genetic issues, environmental exposure to toxins and systemic diseases are just a few of the variables that might cause infertility in men [7].

Objectives of the review article:

a) *This review helps to understand the male infertility.*
b) *Understand what causes male infertility.*

c) *Describe the process associated with evaluation of male infertility.*
d) *Male infertility management in several ways.*

Causes of Infertility

Wide or several numbers of causes are associated with male and female infertility, some of them are as follows [8]:

Men's infertility: causes and effects.

The proportion of several male-specific infertility factors have been shown in figure 1 [9,10]. The percentile of every single factor are as follows such as varicocele is 37%, Idiopathic is 25%, Cryptorchidism is 6%, Obstruction is also 6%, Testicular is failure 9%, Semen disorder is 10%, Others factors are 6% and those other causes includes Abnormal sperm production, Issues with the delivery of sperm, Excess exposure to environmental variables, Damage caused by cancer as shown in Figure 1 [11,12]. Genetic conditions like Klinefelter syndrome, inflammation in Testicular, Undescended testes, Testosterone therapy, Opiate use, Obesity, Anabolic steroid misuse or abuse, Abnormal hormonal function due to genetics, a cancerous or non-cancerous tumour etc. Some major causes are as follows [13]:

a) ***Abnormal sperm production*** *because of undescended testicles, genetic factors/ issues, some medical problems which includes diabetes, diseases like chlamydia, gonorrhoea, measles, and HIV. Varicocele or veins that enlarge within testicles can potentially impair the fertility of sperm [14].*
b) ***Sperm delivery issue*** *is another frequent cause of infertility in men is testosterone delivery issues, that are brought upon by genital disorders such as early ejaculation, rare inheritable diseases like a condition called cystic fibrosis along with anatomical problems, particularly testicular obstruction or damage to the organs that reproduce or female reproductive areas of the body [15].*
c) ***High levels of exposure to environmental variables,*** *is another most important and recent factor nowadays that includes pesticides and various chemicals in addition to radiation [16]. Additionally, some hazardous substances such as Cigarette smoking, marijuana, anabolic steroids or drugs, alcohol used for the treatment of bacterial infections, blood pressure related problems or depression may all have a worst impact on fertility [17].*
d) ***Damage caused on by cancer,*** *or the medications that are prescribed for male infertility i.e. chemotherapy or radiation. The production of sperm can negatively be impacted by chemotherapy [18].*

Female's infertility: causes and effects.

There are several numbers of causes that are associated with female infertility and some of them may include:

a) ***Ovulation disorders*** *could impact the ability of ovary to release eggs. Among these conditions, some are endocrine conditions i.e., polycystic ovary syndrome, [19] Overproduction of the prolactin, hormones which stimulates the breast milk production and may interfere with ovulation and that is known as hyperprolactinemia [20]. The disturbance in menstrual cycle or infertility results from hyperthyroidism or hypothyroidism hormone [21]. In addition to this, certain factors such as Overexertion, eating problems or malignancies may also be underlying factors of this type of female infertility [22].*
b) ***Uterine or cervical abnormalities*** *can be the most important factor that includes abnormalities with cervix part of female reproductive system and shape of the uterus [23]. Also, Non-cancerous tumours in uterine wall may cause infertility in female due to blockage of fallopian tubes as well as retaining a fertilized egg to implant in uterus part of female [25].*
c) ***Damage or blockage of Fallopian tube,*** *inflammation in tube is also known as salpingitis. This tube blockage can result from the pelvic inflammatory disease caused by endometriosis, sexually transmitted infection, or adhesions. These types of causes are very common to see in females [26].*
d) ***Endometriosis,*** *Sometimes the female reproductive part of body may be impacted by endometriosis that develops when endometrial tissue spreads outside the uterus [27].*
e) ***Primary ovarian insufficiency (early menopause),*** *This may be another contributing factor in which when before the age of 40 menstruation stops and the ovaries quit functioning [28]. So, Early menopause has a huge number of risk factors that specially includes immune disorders, genetical problems such as Turner syndrome [29], Fragile X syndrome, chemotherapy treatment and early menopause itself [30].*
f) ***Pelvic adhesions,*** *it may be the factor, but it is uncommon [31]. After pelvic surgery, appendicitis, endometriosis, pelvic infection or sometimes bands of scar tissue that are connected to the organs called pelvic adhesions which can be develop in this disorder [32].*

g) ***Cancer and its treatment,*** *the ability of women to reproduce is commonly impeded by several illnesses, particularly cancers in the reproductive system [33]. Both the therapies i.e., chemotherapy and radiation may have an impact on female fertility [34].*

Symptoms of Male Infertility

There are several symptoms correlated with Male infertility such as Erectile dysfunction, [35] difficulties keeping an erection that can cause issues with sexual function such as problems in ejaculating or sometimes ejaculating lesser amounts of fluid, A testicle-area lump or swelling or pain, Testicles swell or both, change in sexual desire [36], Evacuation issue, Firm testicles, respiratory diseases that reoccur, an inability of smell and many other symptoms [37].

Epidemiology of Male Infertility

In 1866, Matthews Duncan reported the first epidemiological data of infertility study from Scotland [38]. At that time, this was the earliest and until recently it is one of the only population-based investigation into infertility was published in his book Fecundity, Infertility and Sterility [39]. Unfortunately, there weren't many national statistics available on the frequency of infertility [40]. Additionally, census-type data illustrates the proportion of women that are infertile, although the numbers are confounded because of the (unknown) proportion of childlessness that is preferred [41].

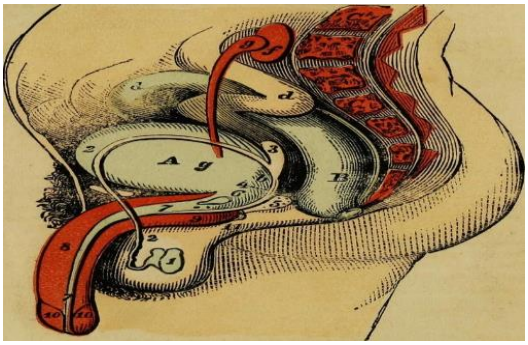

Figure 1. Male Reproductive system (Source: Adapted from Raw pixel under creative commons license)

As a result, while the percentage of women without children has tended to increase over the time and the rate of infertility has changed significantly [42]. Some researchers have revealed that any evident rise in infertility during the 1960s and 1970s was likely caused by voluntary, instead of involuntary [43]. For instance, the voluntary childlessness was widespread in the US throughout the 1920s and 1930s that possibly encompassing 25–40% of childless couples; [44] but after this period the \ voluntary childlessness declined and didn't reappear until the 1960s [45]. Because of the large-scale population-based surveys are uncommon so it is extremely challenging to determine or to evaluate the incidence of the infertility ratio [46]. The National Survey of Family Growth (NSFG) conducted in US is a notable exception. Very few researchers have put forward the fertility problems and should be divided into three groups which are as follows, the first includes those who have become pregnant after a sub fertile episode, "resolved" infertility, and another includes whose infertility is still "unresolved" [47]. Investigations of "infertility" will encompass both individuals deemed sterile as well as those who suffer from diminished reproductive health [48]. The incidence of resolved infertility has been the subject of a lot of discussion in the literature [49]. Primary infertility is estimated to be 5–14% of cases and secondary infertile is 3-12% of cases which is resolved [50]. The Rates of 3-9% and 3-7% respectively, for the primary as well as the secondary infertility have been reported for unresolved infertility [51]. Infertility problems affect 15% of couples worldwide. This indicates that despite trying for a year or longer, about 48 million couples worldwide still struggle to conceive [52]. Almost thirty percent of these instances are the result of male infertility problems. Although there's no way to precisely pinpoint the number of cases of male infertility around the world, recent research carried out by various organisations on a region and country basis have allowed for a better understanding [53]. Infertility affects over 12% of the sexually active population in the USA based according to the CDC [54]. The actual number of cases of infertility may be substantially greater because numerous instances are not reported in many other nations around the world [55].

According to WHO research conducted between 1994 and 2000, fertility rates were highest in North and West Africa, ranging from 4.24 to 6.35%, and lowest in Central and East Asia, ranging from 2.05 to 3.07% [56]. Infertile men are thought to be somewhere between 30,625,864 and 30,641,262 worldwide

[57]. Europe has the greatest prevalence of infertility among men [58]. The African infertile region has a high rate of infertility, according to the WHO report [59].

Variables that could lead to male infertility

There are several risk factors or variables that are associated with both male as well as female infertility and are the almost same [60]. These variables may include:

a) ***Age.*** *After reaching the age of 37, there is a rapid decline in women's fertility due to ageing-related losses [61]. Age-related reproductive declines are most noticeable in the mid-30s [62]. Infertility in older women is primarily caused by a drop in the quantity and quality of eggs, while fertility-related health issues might occasionally play a role [63]. Males over 40 may have lower fertility than those under that age [64].*

b) ***Using tobacco****. Usage of smoking marijuana by each couple reduces their chances of becoming conceived [65]. This can also reduce the expected effectiveness of reproductive therapy [66]. Smokers are more likely to miscarry than non-smokers. Smoking increases a man's risk of developing erectile dysfunction (ED) and low sperm count [67].*

c) ***Using alcohol.*** *Here is no safe level of intake of alcohol for women during pregnancy or fertilisation [68]. Alcohol consumption contributes to infertility. In men, drinking too much can lower the number of sperm and their motility [69].*

d) ***Excess weight.*** *Being inactive and overweight increases the likelihood of infertility in women [70]. A sperm production in man can be additionally affected by his body mass index [71].*

Aetiology of Male Infertility

There are several factors or causes that are interlinked with infertility and they are male factor infertility, ovulatory dysfunction, and tubal disease [72]. Some other factors include Medical, genetic, environment and other causes as discussed below in Table 1. Due to the similar underlying aetiology, numerous causes of male infertility can be roughly divided [88]. The prevalence of these illnesses ranges from 65% to 80% for simple testicular imperfections that require abnormal male reproductive characteristics for no apparent reason, from 2% to 5% for endocrine circumstances, that are usually come on by hypogonadism for 5% for sperm transit disorders, and this require a vasectomy as well as 10% to 20% for irreversible infertility in men of reproductive age despite having adequate testosterone levels and sperm factors [89]. Because of widespread insufficient reporting, cultural variables, including regional variances, precise data are not accessible [90]. Therefore, those are simply broad approximations. Patients who are privately treated might never have the information gathered, but individuals referred to a tertiary referring centre have been more probable to have their health status documented [91].

Table 1: Etiology of Male Infertility

1	**Medical Causes**	Defect in the Sperm, varicocele, troubles ejaculating, anti-sperm antibodies, tumours, infection, undescended testicles, problems with hormones, Defect in the sperm duct, difficulties in sexual activity, specific drugs and the prior surgery can be the examples of medical causes [73].
2	**Genetic Causes**	Chromosome diseases include various disease or syndromes such as translocation, Y chromosome microdeletions, AZFa, AZFb and AZFc deletions, Klinefelter syndrome as well as partial AZF-c deletions [74]. Myotonic dystrophy, sickle cell disease, immotile cilia disorder, mitochondrial deletions and cystic fibrosis are a few examples of conditions that have sexual reversal [75].
3	**Environmental Causes**	Toxins or environmental causes include industrial pollutants, heavy metal exposure, X-rays, scorching the testicles, insecticides, fungicides, and pesticides as well as smoking and excessive alcohol consumption [76].
4	**Endocrinological cause**	These causes include intracranial radiation, Kallmann and Beidl syndrome, head trauma, Prader Willi syndrome, familial cerebellar ataxia, iron overload syndrome, testosterone supplementation [77].
5	**Idiopathic**	In this, infertility is in between 10% to 20% idiopathic where the semen parameters are normal but still the male is unable to fertile [78].

6	**Congenital urogenital abnormalities**	These abnormalities include the Congenital urogenital abnormalities, obstructed epididymis, abnormalities in vas deferens, ejaculatory duct disorders which is also called as cysts [79].
7	**Sexual dysfunction**	Sexual dysfunction includes premature ejaculation, an ejaculation, erectile dysfunction [80].
8	**Acquired urogenital abnormalities**	These types of abnormality include bilateral obstruction, epididymitis, vas deference ligation, Ejaculation retrograde and bilateral orchiectomy [81].
9	**Malignancies**	Malignancies includes craniopharyngiomas, sellar masses, testicular tumours, pituitary macro adenomas or adrenal tumours leading to the excess of androgens [82].
10	**Immunological causes**	These causes include TB, Cysts, lymphocytic hypophysis, histiocytosis, fungal infections, hemosiderosis, sarcoidosis etc [83].
11	**Urogenital tract infections**	Urogenital tract infections or UTI includes chlamydia, syphilis, TB, prostatitis, Gonococci and recurrent prostate vesiculates [84].
12	**Medications or drugs**	Medications that involve male infertility which are psychotropic drugs and leads to inhibition of GnRH and those antagonists are used in prostate carcinoma, some of the alkylating agents, antiandrogen and cimetidine [85].
13	**Genetic causes**	Mutations of cystic fibrosis transmembrane conductance regulator (CFTR), LH, Klinefelter's syndrome, FSH, young syndrome, deficiencies in FGFS, GnRH1/ PROK2R gene, Y chromosome deletion, deletion of GR/GR are included in genetic causes [86].
14	**Other**	Illicit usage of drugs, drinking too much alcohol, smoking, mental anguish and long-distance bicycling [87].

Diagnosed of Male Infertility

a) ***Sperm count (semen analysis).*** *At least two distinct days are used to collect semen samples. Numerous things will be examined by your doctor in the sperm and semen. These variables involve the quantity of semen you produce, its uniformity, and its acidity. They will also take into consideration the amount, shape and mobility of your sperm [92].*

b) ***Blood exams.*** *Doctor will frequently recommend specific blood tests to check hormone levels and identify any further issues [93].*

c) ***Different tests.*** *These tests are conducted by doctors to determine the root cause of male reproductive system problems. For instance, imaging techniques like ultrasounds might be used to inspect the testicle, blood vessels or tissues inside the area known as the scrotum.*

d) ***A biopsy of the testes.*** *Every testicle has a tissue sample taken for examination by a medical practitioner in order to study the semen to identify whether there are indeed any or fewer sperm present. The tool used for examining the sample will be a magnifying lens [94].*

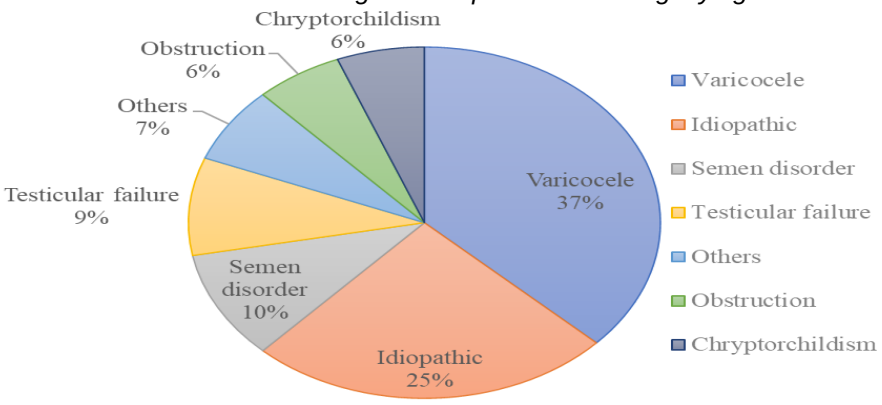

Figure 2: Men's infertility: causes and effects.

Prevention of Male Infertility

There are variety of treatment option available but in some case, infertility is not preventable. For those, which are preventable and having several strategies may increase the chances of pregnancy and they are as follows:

Couples

For the greatest chance of becoming pregnant, can be achieved by engage in regular sexual activity many times near till ovulation. The chances of getting pregnancy increase if you've been having sexual relations for a minimum of five days prior to and leading up to the day of ovulation. The ovulation typically happens in the middle phase or may be 28 days after the last menstrual period in among most women [95].

Men

Mostly every type of infertility is not easily preventable in men but some of these strategies may help regarding this:

a) ***Avoid drug and tobacco use,*** *some changes related to daily life can help in or may contribute to male infertility that are stop drinking more amount of alcohol, smoking, avoid tobacco usage and drugs.*
b) ***Avoid high temperatures,*** *means to avoid the high temperature in hot baths because they can affect the motility as well as temporarily affects the sperm production.*
c) ***Avoid exposure to industrial or environmental toxins,*** *because of environmental toxins it leads to affect the sperm production and avoidance to much exposure is effective in this case [96].*
d) ***Prohibit the usage of some medications that may impact fertility,*** *this may be prescription and non-prescription or both need to be prohibited regarding this. Before takin any kind of medication, always consult to the doctor regularly and prohibit medication without medical officer advice.*
e) ***Exercise moderately.*** *Do much exercise as much as you can. The exercise in daily routine may help in improvement of sperm quality as well as to increase the chances of pregnancy.*

Women

a) ***No to smoking****. In addition to harming your overall well-being and the wellbeing of your foetus, smoking has various detrimental consequences on infertility [97].*
b) ***Alcohol or illegal drugs prohibited****. Such medications might influence how easily one can develop as well as a healthy pregnancy. Avoid alcoholic beverages and illicit substances like cannabis.*
c) ***Limit your caffeine intake.*** *Women that desire to become pregnant might want to regulate the amount of caffeine they consume.*
d) ***Engage in light exercise****. Exercise is important but work out so much that your menstrual cycles are erratic or non-existent, the reproductive system may be damaged. [98].*
e) ***Avoid extremes in weight.***

Treatment options for Infertility

Fertility help

a) ***Fertility help*** *must be the first and foremost approach for treatment that involves helping your partner to get pregnant. This may be through various ways and some of them are as follows:*
b) ***Synthetic fertilisation.*** *The techniques by which healthy sperm injects directly into the partner's uterus or through the cervix's opening. After that sperm can travel via the fallopian tubes through which it reproduces [99].*
c) ***GIFT, IVF, other procedures.*** *In IVF and gamete intra-fallopian transfer (GIFT) work similarly to insemination that is artificial. The following procedure involves fusing your spouse's eggs with a significant amount of superior sperm. The egg and the sperm may be combined in an experimental setting or in the partner's fallopian tube as well [100].*
d) ***ICSI.*** *One sperm is injected onto an egg by partner. After that fertilisation happens beneath the magnifying glass. The fertilised egg is replaced in female by service provider.*

Medicine

If you have a hormone problem that is the root of your infertility, hormone therapy may be able to help. Unbalanced hormone levels can impact sperm development. They could be brought on by an issue with the way the hypothalamus, pituitary, and testes communicate. Antibiotics or gonadotropin therapy are possible treatments [101].

Surgery

Problems that prevent sperm from being produced, maturing, or ejaculating may be fixed surgically. Varicocele surgery, which removes twisted, bulging veins from the scrotum, can occasionally enhance

sperm quality. In addition to this, always consult to healthcare provider regarding any questions or concerns you have about this infertile condition [102].

Recent advancements in male infertility

About 10-15% of infertility cases are active throughout worldwide with the male factors accounting for fifty percent of these cases. Male sub-fertility and infertility have been brought due to several known hereditary, environmental, and medical reasons however because of changes in individuals' lives, there are some other mysterious factors that additionally impact the fertility of men. The best approach for assessing the male fertility is semen analysis, improvements in diagnostic procedures like DNA fragmentation index that can help to understand the reasons of male infertility [103]. Additionally, the likelihood of having an infertile man as a father has considerably improved thanks to reproductive procedures (ART) and new selection of sperms and variety of ART techniques such as Zeta, PICSI and IMSI have strengthened this hope for men. However, these developments in the field have only 10% of infertile men that are able to become fathers, demonstrating that there are still many unanswered questions in this area and a lot of room for advancement, particularly in identifying the factors which affects sperm quality and modifying or eliminating them [104]. To improve the success rate of ARTs, research must uncover novel therapeutic approaches. There must be some advancements in this research are that is as follows:

1. Hazardous substances that lower sperm quality
2. Brand-new pharmaceuticals or phytochemicals that improve sperm quality
3. Newer sperm selection techniques
4. Novel methods with greater likelihood of success for fertility treatments
5. Non-clinical techniques to identify the reasons of male infertility
6. New modifications to the IVF or ICSI procedure to raise the success rate of ART

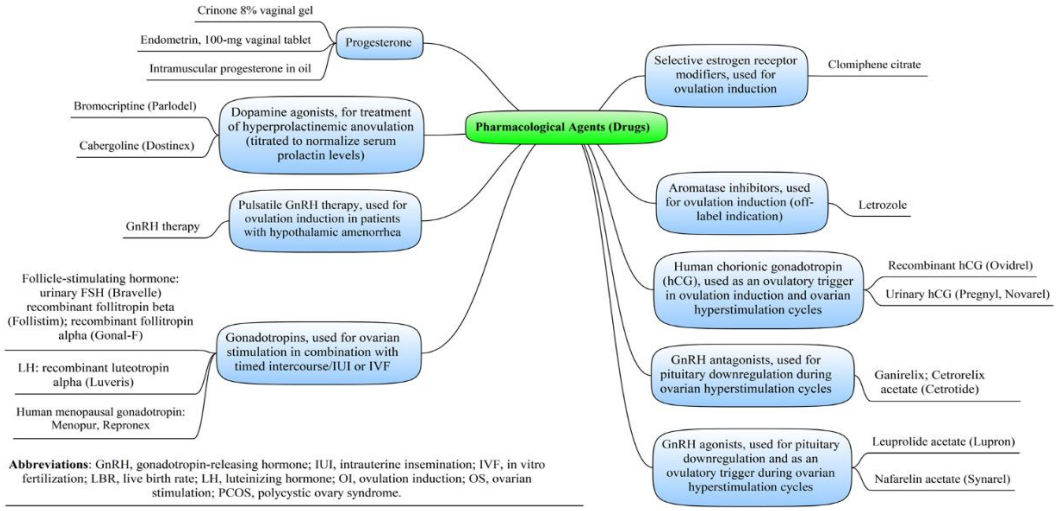

Figure 3. Pharmacological agents or drugs for treatment of infertility

2. CONCLUSION AND DISCUSSION

Infertility is a condition of the male or female reproductive system which is defined by the inability to become pregnant following more than 12 months of unprotected, common, or sexual behaviour. Male fertility arises by a numerous number of reasons that includes both reversible and irreversible diseases. The variety of variables which are involved in male infertility such as age of both partner, usage of drugs or steroids, previous or current surgical history, genetic issues, chemical exposure in the environment and systemic disorders that might have an impact on infertility. After all, one of the few topics on which Darwin and the Bible concur is the requirement of reproduction. Males who are unable to father a kid may feel as though they have failed in one of their most fundamental duties, because of this it leads to depression in some cases and build guilt to male partner for a lifetime. The best approach for assessing the male fertility is semen analysis, improvements in diagnostic procedures like DNA fragmentation index that can help to understand the reasons of male infertility. In addition to this, there are number of techniques for diagnosis and several methods to cure or to prevent for this disorder. Several approaches are yet needs to be done. These all have covered in this article with future perspective and further directions in this research area

Declaration of interest

There is no declaration of Interest.

Funding sources

There is no funding source required in this review.

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