Orient Pharm Exp Med (2017) 17:89–109
DOI 10.1007/s13596-017-0269-7

Online ISSN 2211-1069
Print ISSN 1598-2386

REVIEW

Classification, causes, diagnosis and treatment of male infertility: a review

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Received: 27 February 2017 / Accepted: 3 May 2017 / Published online: 15 June 2017

Abstract Infertility refers to the biological inability of an individual to contribute to conception over the course of one year. Male infertility refers to a male's incapability to cause pregnancy in a fertile female. Approximately 15% of couples are affected by infertility and among them 40–50% cases are attributed to male infertility. Male infertility is mainly categorized into Azoospermia (AS) and Coital infertility (CI). Many studies have supported that different factors such as varicocele, testicular failure, endocrine dysfunction, genital tract infection, testicular disturbances, testicular cancer, hormonal disturbances, retrograde ejaculation, prolonged exposure to heat, obesity, older age, smoking, alcohol, heavy metals, pesticides, oxidative stress, genetic factors and different environmental and nutritional factors reversibly or irreversibly influence male fertility. Male infertility can be diagnosed by different tools. Diagnosing male infertility problems usually involves physical examination, semen analysis, hormone tests, testicular biopsy, urine test etc. There are different pharmacological, non-pharmacological, combination and ethnopharmacological treatment options for male infertility. The infertility of known etiology has considerable treatment success rate. However, genetic or idiopathic male infertility has optimized and empirical approach. This review summarizes classification, causes, diagnosis and treatment of male infertility. The article is based on English peer-reviewed articles located on Scopus, Pubmed, ScienceDirect etc.

Keywords Azoospermia · Coital infertility · Causes · Diagnosis · Male infertility · Treatment

Introduction

According to WHO, "Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year" (WHO 2000). However, Male infertility is incapability of a man to make a fertile woman pregnant (WHO 2010; Olooto 2012). Formerly, a couple's infertility was endorsed to the female only, owing to inadequate knowledge and cultural believe (World Health Organization 2010; Olooto 2012). Around 15% couples are affected by infertility and among them 40–50% cases are attributed to male infertility (De Kretser 1997; Dabaja and Schlegel 2014). Male infertility usually occurs due to acquired or congenital conditions (Ferlin et al. 2007). The cause of infertility in 45% men is unknown (idiopathic infertility) (Jungwirth et al. 2012; Dabaja and Schlegel 2014). Though, 15–30% of male are infertile due to genetic reasons (Ferlin et al. 2007).

To assess infertility in males, the urologist takes case history and performs physical examination including semen analysis (ASRM 2012). After semen analysis, an infertile male may present with following conditions: (a) oligozoospermia (decreased spermatozoa count), (b) teratozoospermia (abnormal sperms), (c) asthenozoospermia (decreased sperm motility). When these abnormalities are found together in semen analysis this condition is called oligo-astheno-teratozoospermia syndrome (Ahmed et al. 2011; Jungwirth et al. 2012). There are various other causes (Fig. 1) and treatment option of male infertility (Sigman et al. 2009). Male infertility of known etiology

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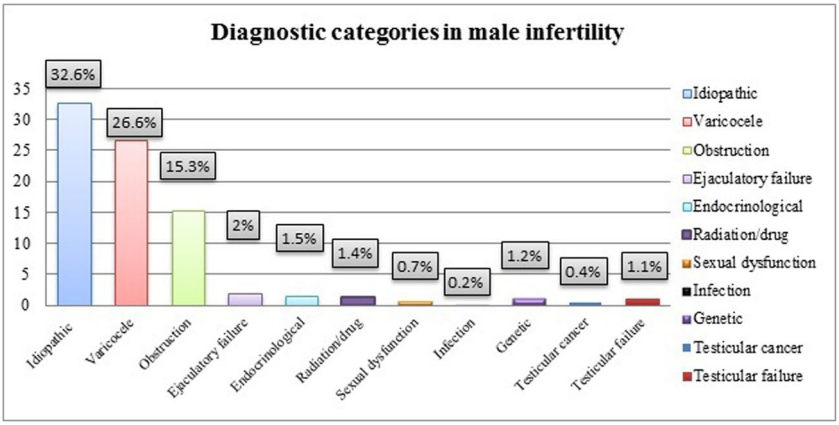

Fig. 1 Various other causes of male infertility

has considerable treatment success rate. However, genetic or idiopathic male infertility has optimized and empirical approach (Jarow and Zirkin 2005; Dabaja and Schlegel 2014).

Classification

Male infertility is mainly categorized into Azoospermia (AS) and Coital infertility (CI). (Raheem and Ralph 2011).

Azoospermia (AS)

AS is complete sperm absence in the ejaculate. It is recognized in 15% infertile men and is classified into Obstructive Infertility (OI) and Non-obstructive Infertility (NOI) (Jungwirth et al. 2012; Cocuzza et al. 2013; Hamada et al. 2013).

Obstructive infertility (OI)

In OI the ejaculate is devoid of spermatozoa with normal spermatogenesis. Approximately 40% of azoospermia cases suffer from OI (Baker and Sabanegh 2013; Hamada et al. 2013; Wosnitzer et al. 2014). OI is characterized by normal endocrine and exocrine system along with normal testes spermatogenesis (Wosnitzer et al. 2014). However, there is an obstruction in the genital tract (GT) (Hamada et al. 2013). It might also occur in any part between ejaculatory ducts and rete testes (Wosnitzer et al. 2014).

Non-obstructive infertility (NOI)

About 60% of azoospermia patients suffer from NOI which is characterized by abnormal spermatogenesis (Kumar 2013; Wosnitzer et al. 2014). It results from primary or secondary testicular failure (TF) or partial or vague testicular failure (Hamada et al. 2013; Kumar 2013; Wosnitzer et al. 2014).

Coital infertility (CI)

It is characterized by normal sperm production and genital tract. Yet, the illness is secondary to patient's sexual dysfunction, that effects ejaculation (Raheem and Raph 2001).

Causes of male infertility

Male infertility can be due to multiple reasons including; varicocele (enlargement of spermatic veins), testicular failure, endocrine dysfunction, genital tract infection, testicular disturbances, testicular cancer, exposure to gonadotoxic substances (Table 1) (Nieschlag 2000; Cocuzza et al. 2013; Kupis et al. 2015), prolonged exposure to heat, obesity, smoking, older age, hormonal disturbances, retrograde ejaculation (ReE), impotence (Fode et al. 2012; Harlev et al. 2015), environmental pollutants (i.e. lead, paint, radiations, pesticides) (Jensen et al. 2006; Pizent et al. 2012), wearing tight underwear (increases scrotal temperature results in decreasing the sperm production) (Jung and Schuppe 2006), inadequate zinc (Zn) and vitamin C in diet, excessive stress, malnutrition, anemia and use of certain drugs including nitrofurantoin, spironolactone and cemitidine (Arcaniolo et al. 2014; Kolesnikova et al. 2015).

Causes of obstructive infertility

Ejaculatory duct obstruction (EDO)

EDO associated with infertility, is an eminent but occasional cause of obstructive Infertility reported in 5% cases (McQuaid and Tanrikut 2013; Velasquez and Tanrikut 2014). It may be acquired or congenital. Congenital cases are characterized by stenosis or atresia along with cystic lesions. Acquired reasons might be inflammation or trauma with calculus and stenosis following prostatic transurethral resection (Schroeder-Printzen et al. 2000). Typical EDO is characterized by acidic ejaculate, normal hormones, dilated ejaculatory ducts and

Table 1 Major causes of male infertility

Causes of obstructive infertility	Causes of non-obstructive infertility	Causes of coital infertility
Ejaculatory duct obstruction	Cryptorchidism	Penile deformities
Epidydimal obstruction	Testicular torsion	Premature ejaculation
Vasectomy	Testicular trauma	Retrograde ejaculation
Vassal obstruction	Testicular cancer	Anejaculation
Congenital absence of vas deferens	Varicocele	Erectile dysfunction
	Genetic factors Hormonal imbalance	
	Immunologic infertility	
	Exposure to gonadotoxins	

seminal vesicles, dysuria, painful ejaculation, prostatic calcification or cysts and hematospermia (Velasquez and Tanrikut 2014). Obstruction may be complete or partial; person with complete duct obstruction presents total absence of sperm in the ejaculate and person with partial duct obstruction have reduced number of sperms in the ejaculate (Roberts and Jarvi 2009; Velasquez and Tanrikut 2014). Only 1% infertile males have been reported to be suffering from complete EDO (Lee et al. 2013).

Epididymal obstruction

Epididymis is a tightly coiled narrow tube connecting efferent ductules to the vas deferens. It is responsible for maturation, transportation and storage of sperms (Hermo et al. 2008). Any inflammation, blockage or disease in the duct can affect the maturation, transportation and storage of sperms and hence can cause male infertility (Azenabor et al. 2015). About 30–67% of AS cases suffer from epididymal obstruction (WHO 2000). Epididymal obstruction is usually caused by infections in epididymis (Ammar et al. 2012). Epididymal surgery, for instance cyst removal may result in azoospermia. Moreover, distal obstruction leading to epididymal obstruction should also be considered while treating seminal ducts (Cocuzza et al. 2013).

Vasectomy

It is a simple and an effective surgical technique of contraception in males, with 1% failure ratio (Rayala and Viera 2013; Jung and Ju 2014). Ideally, vasectomy is characterized by reversible AS and lack of adverse effects (Jung and Ju 2014). About 60 million males use this contraception technique (Parekattil and Gudeloglu 2013). It is a leading cause of OI and may damage functions of epididymal epithelial with epididymal obstruction (Jequie 1998; Baker and Sabanegh 2013). It may result in 20 to 40% decrease in spermatids count, after 1 to 20 years of the procedure (Raleigh et al. 2004; Xiang et al. 2013). However; 2–6% males undergo vasectomy reversal procedure (Vasovasostomy) within 10 years, desiring to develop fertility again (Dohle et al. 2012; Parekattil and Gudeloglu 2013).

Causes of non-obstructive infertility

Cryptorchidism

It is an inability of testes to descend down into scrotum, reported in about 2 to 6% newborns (Datta et al. 2013; Fawzy et al. 2015). Nearly, 10% infertile individuals suffer from cryptorchidism (Fawzy et al. 2015). In bilateral cryptorchidism (BCr), both testes remain in abdominal cavity that eventually causes complete sterility. However, in unilateral cryptorchidism (UCr), one testis remains in abdominal cavity and other remains normal and descends down to scrotal sac. The normal one performs steroidogenesis and spermatogenesis in usual way, however at reduced level (Datta et al. 2013). There is 13% prevalence rate of OA in UCr and 89% in BCr, thus making it foremost etiological cause of NOI in adults (Wood and Elder 2009; Docampo and Hadziselimovic 2015). Cryptorchidism is a multifactorial disorder, producing detrimental impact on reproductive functioning with great risk of testicular cancer and epididymal abnormality (Virtanen et al. 2005; Singh et al. 2012; Datta et al. 2013). There are 13 to 34% chances of developing azoospermia, even after treatment of both types of cryptorchidism. Though, 30 to 80% cases of AS are the consequence of untreated cryptorchidism (Cocuzza et al. 2013).

Testicular torsion (TT)

It is a critical andrological and urological emergency characterized by twisty spermatic cord, with decrease or blocked blood supply, causing severe pain, testicle ischemia/infarction and may consequently result in testicle loss (Sandella et al. 2012; Singh et al. 2012). The disease occurs in two age groups; new born and adolescents (usually between 12 and 18 years) (Jain and Viswanath 2014). It is among foremost causes of male infertility. Infertile males represent long term outcomes of the disease at young age than with

the acute TT itself. These long-term outcomes include; acquired anorchia, testicular atrophy, oligoasthenoteratospermia, oligozoospermia, and non-obstructive infertility (Singh et al. 2012). Even with low incidence (0.1–1.2%) of TT in infertile males, 40 to 70% men suffering from TT represent abnormal semen parameters (Callewaert and Van 2010; Singh et al. 2012).

Testicular trauma

Testicular trauma is characterized by swelling and dislocation or disruption of testicles, which can result from some accident or injury to the testicles (Mulhall et al. 1995). Injury to testicles can result in bleeding and formation of anti-sperm antibodies which can eventually lead to infertility (Kukadia et al. 1996). Sometimes injured testes may cause male infertility (Hagiuda et al. 2014). It is one of the etiological causes of non-obstructive infertility (Esteves 2015).

Testicular cancer

It is an abnormal growth on testes which appears as a painless lump on the surface of testes. Cancer on one testis may not affect male fertility. However, males having testicular cancer have lower fertility (Moller and Skakkebaek 1999). It is a treatable cancer, with 95% survival rate. Treatment of gonadotoxic cancer compromises fertility, either permanently or temporarily. It causes infertility because of ejaculatory dysfunction as a consequence of pelvic plexus (Ping et al. 2014). In such patients fertility is further affected by exposure to chemotherapy or radiotherapy (Moller and Skakkebaek 1999). There is an association between testicular cancer and infertility. Contralateral testes size is small in infertile individuals suffering from testicular cancer. In these patients if there is obstructive infertility and non-obstructive infertility, fertilization is characterized by sperm extraction (Skakkebaek et al. 2001; Carmignani et al. 2007).

Varicocele

It is the dilatation of scrotal veins. Approximately 15% men are affected by this condition and among them 40% are infertile (Nagler et al. 1997). It is characterized by scrotal swelling and pain. Several studies have demonstrated abnormal semen parameters in patients affected by varicocele. MacLeod (1965) has reported that majority semen samples of patients affected by varicocele had decreased no. of sperms, decreased motility and abnormal morphology (MacLeod 1965). The mechanisms which may cause varicocele include hypoxia, testicular venous hypertension, increased spermatic vein catecholamine, increased testicular temperature and increased oxidative stress. It is a common etiological factor of infertility (Kantartzi et al. 2007). Frequency of varicocele in azoospermia patients is 5% to 10% (Cocuzza et al. 2008). Approximately, 22% men with non-obstructive infertility had both immotile and motile spermatozoa in the ejaculate within 14.7 months of varicocele treatment; however, 9.6% patients had adequate motile spermatozoa (Kantartzi et al. 2007).

Genetic factors

It is a major contributing factor in male infertility, which can influence hormonal homeostasis, spermatogenesis and sperm quality (Poongothai et al. 2009). Genetic causes of infertility may include chromosomal abnormalities, autosomal gene mutation, polymorphism and epigenetic errors (Carrell 2008; Poongothai et al. 2009). Some researchers have suggested that non-obstructive infertility mainly results from genetic factors (Lu et al. 2014). Chromosomal abnormalities frequently cause aneuploidy in infertile men (Emery and Carrell 2006). Patients of non-obstructive infertility have high aneuploidy rate, particularly in sex chromosomes (Mateizel et al. 2002; Palermo et al. 2002). Such patients fertilize oocyte with infrequent success and can transfer incorrect number of chromosomes to offspring (Carrell 2008). Klinefelter syndrome is a common chromosomal abnormality due to aneuploidy, with 10% prevalence rate in azoospermic individuals and 5% in individuals with oligozoospermia (Foresta et al. 2005).

Hormonal imbalance

Any fluctuation in the level of hormones in human body can affect fertility and reproductive system of both male and female (Kumar 2013). This hormonal imbalance may be caused by genetic condition, gland malfunction and unhealthy weight; these factors can interfere with the production of sperm and ultimately can influence male fertility (Poongothai et al. 2009). Any fluctuation in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone can affect spermatogenesis in males. High FSH level or lack of typical spermatogenesis due to testicular histology in azoospermia is an evidence of non-obstructive infertility (Finkel et al. 1985; Kumar 2013). Testosterone is involved in the development of scrotum, penis and prostate. Intracellularly it is required to maintain the spermatogenesis and to inhibit apoptosis of germ cells. Level of testosterone is decreased in old age and in obese persons, which causes erectile dysfunction and low sex drive (Singh et al. 1995). Moreover, hypothyroidism or hyperthyroidism also affects male reproductive system. Studies have demonstrated that hypothyroidism decreases the level of serum testosterone and gonadotropins (GTs) which ultimately affect spermatogenesis (Krassas et al. 2010).

Immunologic infertility

It is an autoimmune condition involving both cellular and humoral immune system. Still, its mechanism is not distinctly understood (Kobayashi et al. 2012). Sperm is antigenic, even though immune system does not target human sperms normally. However, sperm antigens when interaction with the immune cells, form antisperm antibodies (ASAs). In azoospermia, there may be breakage of blood-testis barrier and immune system might interacts sperm cells thus producing ASA. There is 5% more risks of producing ASAs in infertile pairs than fertile ones (Chamley and Clarke 2007; Zangbar et al. 2016). Approximately, 11% TT patients represent ASAs at the time or after torsion. ASAs also cause asthenospermia (defects of sperm movement) (Kobayashi et al. 2012).

Causes of coital infertility

Penile deformities

Person with abnormal position of urethra meatus or with congenital penile curvature can have problem in vaginal penetration and sperm discharge. Penile abnormalities include phimosis, hypospadias, penile deviation and epispadia. Infertile patients suffering from these abnormalities might have decreased fertility or coital infertility (Abdel-Raheem et al. 2012).

Premature ejaculation (PE)

PE is that ejaculation which occurs before or within one minute of vaginal penetration (Abdel-Raheem et al. 2012; Jungwirth et al. 2012). It is related with poor relationship satisfaction (Shindel et al. 2008). Frequency and characteristics of PE have poorly explored in infertile patients. It has been reported in one in every six patients. It is a common sexual dysfunction that may cause male infertility or CI (Abdel-Raheem et al. 2012; Lotti et al. 2012).

Retrograde ejaculation (ReE)

In ReE, there is partial or complete sperms ejaculation into bladder instead of urethra and penis (Barazani et al. 2012). When sperms mix up with urine, they don't survive very long. It results from anatomic, neurogenic and pharmacological factors (Kamischke and Nieschlag 2002; Barazani et al. 2012). Pharmacologically it is attributable to alpha blockers and psychotropic drugs (Abdel-Raheem et al. 2012). Neurogenic reasons include lesions of spinal cord, retroperitoneal surgery and neuropathies (multiple sclerosis and diabetic neuropathy) (Barazani et al. 2012). Usually, it is caused by same causes as of anejaculation (AnE) but at minor degree. It may also result after prostate's transurethral resection. Sperm in post orgasmic urine sample is a particular indicator of ReE (Kaplan 2009; Abdel-Raheem et al. 2012). It is a rare cause of infertility (Yavetz et al. 1994, Ohl et al. 2008). Yet, it is suspected to cause azoospermia, particularly coital infertility (Yavetz et al. 1994; Abdel-Raheem et al. 2012).

Anejaculation (AnE)

It is an inability to ejaculate even with normal erection (Rowland et al. 2010; Salama 2015). It is a rare cause of male infertility reported in only 2% cases. Yet it is an important etiological factor for coital infertility (Salama 2015). AnE is characterized by lack of retrograde ejaculation or antegrade ejaculation, owing to failure of releasing semen from ejaculatory ducts, prostate and seminal vesicles into urethra (Fode et al. 2012; Jungwirth et al. 2012). True AnE, accompanying normal sensation of orgasmic is associated with drugs (antidepressants/alpha blockers) and nervous system dysfunction (Abdel-Raheem et al. 2012; Jungwirth et al. 2012). It may be caused by neurological disorders including spinal cord injury (SpCI) (Fode et al. 2012). Primary AnE, may results from psychosexual or neurological factors such e.g., decreased genital organs sensitivity or high ejaculatory reflex threshold. Secondary AnE, may follows surgeries of abdomen or pelvis that originate sympathetic chain injury. It may occur in diabetic autonomic neuropathy and in other types of autonomic neuropathy (Ohl et al. 2008; Abdel-Raheem et al. 2012). Table 2 represents different causes of anejaculation.

Other causes of male infertility

Age

Many studies have reported decrease in male fertility with increase in age due to changes in all sperm parameters (Kidd et al. 2001; Harris et al. 2011). With the increasing age there is reduction in sperm concentration, sperm motility and seminal volume (Pasqualotto et al. 2005; Harris et al. 2009). Older individuals have anomalous sperm morphology i.e., less normal sperm forms with decreased vitality along with supplementary cytoplasmic droplets (Ng et al. 2004; Pasqualotto et al. 2005). Erectile dysfunction (EDF) is also common in aged men. The prevalence of EDF is more with increasing age. Approximately 40% men of age 40 suffer from EDF.

Table 2 Causes of anejaculation

Anatomic	Congenital abnormalities, pelvic radiation, bladder neck Y-V plasty
Drugs	Antipsychotics, alpha adrenergic blockers, antidepressant
Neurogenic	Multiple sclerosis, diabetes, thoracic spinal surgery, spinal cord injury

The percentage escalates to almost 70% in the age of 70 years. Occurrence of complete EDF upsurges from 5% to 15% with increasing age from 40 to 70 years (Feldman et al. 1994). Over time, with increasing age there are endocrine and morphological modifications in testes and the possibilities of miscarriage and offspring genetic abnormalities increase (Pasqualotto et al. 2005).

Genital tract infections (GTI)

Different types of viral and bacterial infections can influence male fertility by reducing sperm viability. *S. aureus* and *E. coli* found in male semen may result in primary infertility (Momoh et al. 2017). Moreover, mymcoplasmas and ureaplasmas might colonize urethra and infect semen. Ureaplasma urealyticum (UU) is pathogenic and causes GTI leading to male infertility (Moretti et al. 2009). It induces leukocytospermia which lead to decrease sperm counts, sperm damage and invariably impaired sperm motility (Wolf 1995). Herpes simplex virus (HSV) found in semen may cause low sperm count, reduce sperm motility and sperm damage (Momoh et al. 2017).

Sexually transmitted diseases (STD_s)

STD_s are caused by bacteria, viruses and parasitic microorganisms. These diseases are; syphilis, Chlamydia, gonorrhea, chancroid and trichomoniasis. Human papillomavirus, lymphogranuloma venereum and HSV also cause STD_s (Junior et al. 2009). If not treated on time they may lead to irreversible infertility (Ochsedorf 2008). STD_s may result in poor quality sperm and reduced sperm motility and concentration. However, these effects on semen are unclear. Chronic infections are more likely cause of infertility than acute ones (Gimenes et al. 2014).

Malnutrition

There is an instinctive relationship between reproduction and nutrition (Triunfo and Lanzone 2015; Wong et al. 2000). Nutrition has a vital role in sperm quality (Gaskins et al. 2012). However, the effect of nutrition on male infertility needs an extensive research. Malnutrition might be an imperative cause of male infertility (Wong et al. 2000). It adversely harms sperm functioning (Harris et al. 2011). Prolonged starvation and excessive exercise can affect sperm count, motility and even can stop sperm production (Gaskins et al. 2012; Sharma et al. 2013). Excessive restriction in food intake can reduce the level of Zn, vitamin C, vitmin A, vitamin E, selenium (Se), folic acid and other nutrients that are necessary for proper functioning of body and spermatogenesis (Wong et al. 2002; Kobori et al. 2014). Deficiency of these elements can affect various semen parameters (Kobori et al. 2014).

Psychological stress

It is an uncomfortable emotional state accompanying behavioral, biochemical and physiological changes (Nargund 2015). Stress; whether social, psychological or physical is an attention seeking element of society (Sharma et al. 2013). Different studies have suggested that psychological stress plays a key role in male infertility (Collodel et al. 2008; Sharma et al. 2013). In males, it increases glucocorticoid level which suppresses testosterone concentration in testes (Whirledge and John 2010) that rigorously affecting spermatogenesis (Nargund 2015). Stress may also induce structural and meiotic changes in sperm and make it difficult to target ovum (Collodel et al. 2008; Sultan and Tahir 2011). Infertility may result in stress, depression, low self-esteem, negative thoughts and marital problem (Rauf and Salma 2015).

Drugs

Impaired reproduction is a multifactorial problem. Some drugs are also involved in causing male infertility. Sulfasalazine is a disease anti rheumatic drug, which is known to reduce male fertility. Methotrexate is an immunosuppressive drug that alters semen quality (Brydøy et al. 2007; Silva et al. 2010). Methotrexate is responsible for the inhibition of dihydrofolate reductase enzyme which is important for folate synthesis. Folate is required for the synthesis of thymidine which is an important component of RNA and DNA protein synthesis. Deficiency of folate leads to suppression of many cellular processes important for sperm development. Methotrexate also induce germ cell apoptosis by increasing the level of Bax/Bcl-2 (Morris et al. 1993). Use of beta blockers and some psychotropic drugs can cause impotence in males. Other drugs with high risk of infertility are; cyclophosphamide, chlorambucil, melphalan, procarbazine, bleomycin and dactinomycin (Brydøy et al. 2007; Abdel-Raheem et al. 2012).

Chemical agents

Heavy metals Some metals including lead, chromium, copper and cadmium adversely affect sperm and male reproductive system (Jelnes et al. 1988; Tchounwou et al. 2012). The magnitude of effect is directly associated with concentrations and exposure duration (Vigeh et al. 2011). Increase level of these metals in the blood affect male fertility, by decreasing the sperm count, reducing sperm quality and altering its morphology (Jelnes et al. 1988; Tchounwou et al. 2012). Welders are more exposed to radiant heat, deleterious metals and harmful gases (Kumar et al. 2003) and have lesser sperm count and viable sperms. This is probably due to their exposure tochromium which diminishes both sperm quantity and quality (Vigeh et al. 2011; Pizent et al. 2012).

Pesticides Rate of male fertility is declining worldwide. Pesticides are another contributing factor in male infertility. Experimental evidences have shown that chemicals present in pesticides can cause testicular cancer, reduce sperm quality and erectile dysfunction (Tielemans et al. 1999; Kaur et al. 2015). Individuals exposed to pesticides have high risk of primary and secondary infertility (Kaur et al. 2015). These chemicals may block the activity of hormones i.e. androgens, testosterones, and gonadotropins which influence male reproductive system (Tielemans et al. 1999).

Excessive heat

Spermatogenesis is influenced by temperature. Testicles lie outside the body in scrotum, because production of active sperms requires 3–4 °C lower temperature than body temperature (Mieusset and Bujan 1995; Durairajanayagam et al. 2015). Testicular hyperthermia can cause the genital heat stress leading to the production of low quality spermatozoa. Heat exposure can lead to many abnormalities in the testis including; dilatation of smooth endoplasmic reticulum, degeneration of mitochondria and wider spaces in spermatid cells. Heat stress leads to damage DNA, autophagy and apoptosis of germ cells due to generation of reactive oxygen species and breakage of strands (Kanter et al. 2013).

Posture and clothing Testicular temperature is influenced by scrotal position. It changes with the change in posture. Scrotal temperature is low on a naked and upright body (Zorgniotti and Macleod 1973; Durairajanayagam et al. 2015). Researchers have shown that wearing tight clothing and tight underwear also increases scrotal temperature (Jung and Schuppe 2006).

Exercise Excessive exercise can also elevate body temperature of men's testicles and hence can cause hyperthermia which subsequently produces heat stress of germ cells and sperm damage (Durairajanayagam et al. 2015). Among exercises, frequent bike riding and cycling can also increase testicles temperature, due to body posture, intensity and duration of ride or cycling (Jung et al. 2008).

Laptop use Men who keep their laptops on their legs are also at high risk of infertility problems because of increased scrotal temperature due to heat from pressing of legs together and the heat from laptop (Sheynkin et al. 2005).

Seasonal temperature Seasonal temperature affects sperm concentration, motility and morphology (Durairajanayagam et al. 2015). There are evidences on reduction of sperm count in summer. Researchers have reported that it varies by 70% in winter (Jorgensen et al. 2001).

Smoking

There is evidence that male fertility is affected by smoking (Wong et al. 2000; Homan et al. 2007). There is high concentration of free radicals in the seminal fluid of smokers (Abdel-Raheem et al. 2012; Schilling et al. 2012), which causes sperm damage and production of high concentration of malformed sperms (Schilling et al. 2012). Cigarette smoke is a vital source of non-occupational exposure to metals that produces hazardous effects on male fertility. It comprises of approximately 30 toxic metals, among them lead, cadmium and arsenic are in great concentrations (Pizent et al. 2012). Cigarette is also a source of nicotine. Byproducts of nicotine reduce the fertilization capacity of sperm by reducing the motility of sperms (Schilling et al. 2012). Tobacco smoking also increases cadmium concentration in seminal plasma and may perhaps harmfully affect reproductive function in males (Pizent et al. 2012).

Alcohol

Use of alcohol adversely affects male reproductive system in a number of ways (Platz et al. 2004; Pizent et al. 2012). Many evidences have shown that excessive intake of alcohol in men causes shrinkage of testes and impairs production of testosterone hence resulting in infertility, impotence, decreased libido and reduction of secondary sexual characteristics (Onyije 2012). Alcohol also causes testicular atrophy by effecting LH and FSH (Dosumu et al. 2014). It also affectssexual performance by depressing central nervous system thus causing difficulty in erection and controlling ejaculation (Wong et al. 2000). Vitamin A governs spermatogonial differentiation as well as normal sperm count (Hogarth et al. 2011). Alcohol decreases the metabolism of vitamin A in liver (Clugston and Blaner 2012) due to which there is impairment in sperms development (Hogarth et al. 2011).

Obesity

Obesity adversely affects male fertility by suppressing spermatogenesis and sperm morphological changes (Jensen et al. 2004; Ivell 2007). Recent study of World Health Organization has confirmed that sperm count is less in obese men than non-obese men. Obesity effect fertility of men by changing hormonal profile, increasing scrotal temperature and altered semen parameters (Stefan et al. 2010). Some studies have directly correlated obesity with erectile dysfunction and decreased libido (Tamler 2009). In obese men, there is increase distribution of fat in upper thighs, scrotum and suprapubic area, which is associated with increase testicular temperature that affects spermatogenesis (Kort et al. 2006; Durairajanayagam et al. 2015). Men with body mass index (BMI) ≥25 had 25% low sperm count than men with normal BMI (Chavarro et al. 2009;

Durairajanayagam et al. 2015). Increased body weight also influences sperms motility i.e. increase in BMI decreases sperms motility (Jensen et al. 2004).

Oxidative stress

Reactive oxygen species (ROS) are necessary for the performance of normal physiological functions of a cell (Agarwal et al. 2003). Inside the cell, ROS are found as free radicals, these free radicals include superoxide, hydroxyl ion, hydrogen peroxide (H_2O_2), hypochlorite ion and peroxyl radicals (Walczak-Jedrzejowska et al. 2012). Occasionally, excessive ROS are considered to be harmful for the survival of sperm (Choudhary et al. 2010). Increased H_2O_2 concentration causes immobilization of sperms by decreasing ATP level and lipid peroxidation (Choudhary et al. 2010). ROS are also associated with DNA damage and apoptosis inside the sperms (Fraczek and Kurpisz 2005; Schuppe et al. 2008) by disruption of mitochondrial membrane that causes the release of Cytochrome-C hence leading to apoptosis and DNA fragmentation inside cell nucleus (Sharma et al. 2004; Walczak-Jedrzejowska et al. 2012).

Diagnostic tools for male infertility

There has been significant advancement in diagnosis of male infertility in previous few years. For diagnosis, the fertility state of female partner should be considered, for determining the final outcome (ASRM 2012; Jungwirth et al. 2012).

Physical examination

Case history and physical examination are important tools for the disease assessment (ASRM 2012). It involves patient questioning, genital examination including prostate, anal sphincter tone and bulbocavernosus reflex evaluation. Physical examination involves assessment of: cryptorchidism (UCr/BCr), genital tract infection, testicular cancer, testicular torsion, testicular trauma, absence of testes, gynaecomastia, varicocele, abnormal sexual characteristics and abnormal testicular volume or consistency (Jungwirth et al. 2012; Singh et al. 2012).

Semen analysis

It is a main tool for analysis of male infertility. It should essentially be carried out at high standards to estimate all parameters of male ejaculate (Table 3). It is performed to analyze the shape, movement and number of sperms under microscope as well as sperm production (Patil et al. 2013; Vasan 2011). It is preferred to collect the sample in a room close to laboratory.

Table 3 Lower reference values of semen characteristics

Parameter	Lower reference value
Semen volume (ml)	1.5
Total sperm count (millions/ejaculate)	39
Total motility (%)	40
Progressive motility (%)	32
Vitality (live spermatozoa) (%)	58
Normal forms (%)	4
pH	7.2
Seminal Zn (mg/L)	78.9
Seminal fructose (μg/ml)	1200

Though, commonly it has been reported that patients feel comfortable at home in producing the sample. However in that case, the sample must be taken to lab within 2–3 h and maintained at 20 °C prior to analysis (Jequier 2010). Staining of seminal smear permits quantitative assessment of both normal and abnormal morphological forms of sperm in the ejaculate (Menkveld et al. 1990). In non-obstructive infertility, semen analysis displays normal ejaculate volume after centrifugation. The recommended technique is sample centrifugation for 15 min at 3000 g and microscopic investigation at ×200 magnification by phase contrast (Vasan 2011; Jungwirth et al. 2012).

Hormone tests

Hormonal imbalance can also cause male infertility. It can be checked from blood sample (Poongothai et al. 2009; Kumar 2013). The test is limited in determining the levels of testosterone, LH and FSH. It is performed in individuals with possibility of hypogonadism. The differentiation between obstructive infertility and non-obstructive infertility is a significant factor in male infertility. In obstruction there is normal level of FSH with bilaterally standard testicular volume. Yet, 29% individuals having normal FSH are characterized by defective spermatogenesis or spermatogenic arrest (Weber et al. 2005; Jungwirth et al. 2012).

Testicular biopsy (TBO)

TBO is the only technique for testicular histopathology (Madbouly et al. 2012). The biopsy is performed under anesthesia. Bilateral TBO is recommended while diagnosing male infertility (Nistal and Paniagua 1999). It is predominantly useful for investigation of oligospermia and AS with normal endocrine activity. TBO for oligospermia and AS represents altered pathological patterns (Abdullah and Bondagji 2011). Among different patterns, hypospermatogenesis is the common spermatogenic defect pattern (Abdullah and Bondagji 2011).

Though *sertoli cell only* (SCO) histology is a common pattern in individuals with AS, small testes, primary infertility and primary testicular failure. High LH and FSH and Low testicular volume are associated with compromised spermatogenesis (Madbouly et al. 2012). Men with ≥7.6 mIU/ml FSH or ≤4.6 cm testicular long axis suffer from NOI. However, Men with ≤7.6 mIU/ml FSH or ≥4.6 cm testicular long axis may undergo reconstructive surgery either with or without TBO and sperm extraction, or TBO only (Schoor et al. 2002).

Urine test

This is a non-invasive and cost effective technique for screening males with reproductive impairment. The test is for total FSH in urine and is decidedly sensitive to identify males with high serum FSH. Men with low urine FSH, also represent low serum FSH (Wang et al. 1999; Madbouly et al. 2012). Serum FSH increases in testicular failure which causes azoospermia. Post ejaculation urine assessment can also identify men with retrograde ejaculation. (Gudeloglu and Sijo 2013). However, the test loses it sensitivity when applied to males of less sperm production as such individuals do not have sufficient testicular failure that causes pituitary GT selevation (Wang et al. 1999; Krassas and Perros 2003). An additional complication ensues when an individual is with less sperm counts for other reason than gonadal failure, like reproductive tract blockage. The test has good negative prognostic value for detecting individuals without less sperm counts (Overstreet 1984). The test is noteworthy for individuals in whom labor-intensive semen studies are not practicable (Wang et al. 1999).

Treatment

Male infertility treatment is aimed to normalize or improve fertility state of the patient (Kumar et al. 2003). Though, it is frustrating owing to inadequate knowledge of male reproductive functions, pathophysiology and less specific or empirical pharmacological approach. However, the treatment practice has improved with time (Jarow and Zirkin 2005; Dabaja and Schlegel 2014). Various treatment options for male infertility are mentioned in Fig. 2.

Pharmacological treatment

Hormonal treatment

Gonadotrophin releasing hormone (GnRH) Idiopathic infertility is most commonly treated with GnRH. GnRH stimulates the release of LH and FSH by estrogen receptors blockade in hypothalamus (Safeer zaman et al. 2009). Pulsatile treatment with GnRH, substitutes GnRH deficiency in infertile individuals suffering from hypogonadotropic hypogonadism (H_GH) and lack of hypothalamus secretions. Individuals with H_GH have reduced fertility status that is restored by FSH stimulation (Dabaja and Schlegel 2014).

Gonadotropins (GTs) Human chorionic gonadotropin (rec-hCG), LH (rec-hLH), FSH (rec-hFSH) and purified urinary GTs are used for the treatment of infertile men with pituitary inefficiency. They persuade spermatogenesis in around 80% treated individuals (ASRM 2012; Dabaja and Schlegel 2014). GTs are self-administered via subcutaneous (s.c.) injections. Treatment duration differs from 6 to 24 months until sperm appearance in ejaculate or until pregnancy (Burgués and Calderón 1997).

Dopamine agonists

Hypothalamus releases dopamine which causes inhibition of prolactin from anterior pituitary. Dopamine agonists, treat male infertility caused by hyperprolactinemia. However, they have little potential for treating idiopathic infertility (Liu and David 2003). Bromocriptine and cabergoline are two dopamine agonists that have comprehensively studied for hyperprolactinemia (De Rosa et al. 2003). Cabergoline has more ability to normalize prolactin levels than bromocriptine. There is earlier improvement of sexual and gonadal function in men with prolactinoma, by cabergoline than bromocriptine (Barlier and Jaquet 2006).

Estrogen receptor antagonist and aromatase inhibitors (A_RInh)

In males A_RInh delay epiphysial maturation and increase testosterone levels (Ronde and Frank 2011). Most of the estrogen is produced in fat cells, where aromatase enzyme converts the circulating testosterone into estrogen (Simpson and Davis 2001). In obese men excessive estrogen is produced by this testosterone conversion process. Any alteration in the ratio of estrogen and testosterone can decrease the pituitary level of FSH and LH and can influence the sperm production (Raven et al. 2006). Estrogen receptor antagonists are also known as antiestrogens (Hamada et al. 2012). Clomiphene and tamoxifen are two most commonly used antiestrogens for male infertility. Clomiphene increases the serum level of FSH, LH and testosterone (Zaman et al. 2009). Both antiestrogensand A_RInh effect estrogen's negative feedback and increase LH and FSH

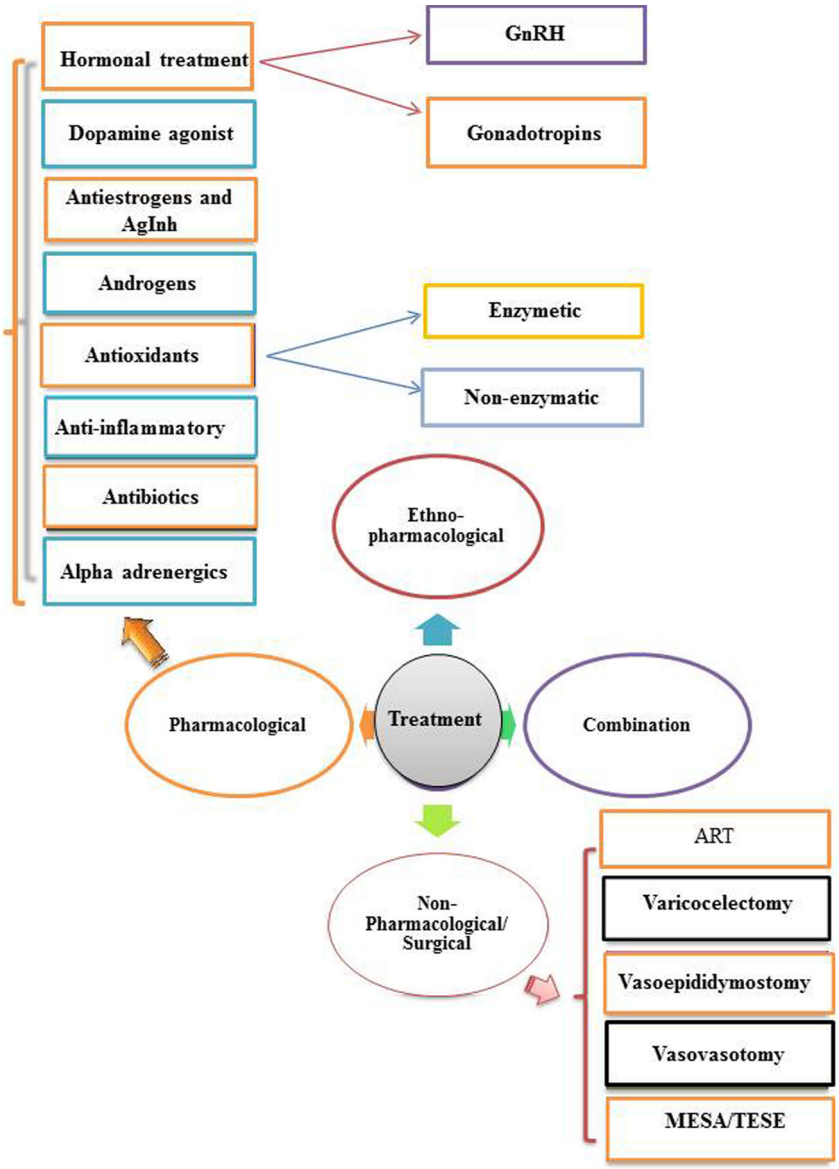

Fig. 2 Various treatment options for male infertility

levels which then increases steroidogenesis and spermatogenesis (Hamada et al. 2012).

Androgens

Testosterone is contraceptive due to feedback inhibition thus it overwhelms spermatogenesis and non-obstructive infertility that is medically amenable (Hamada et al. 2012). It is a sort of H_GH, in which excessive androgens results in, feedback inhibition on gonadotropin secretion (LH and FSH), and suppression of steroids that consequently recovers spermatogenesis (Kumar 2013). The purpose of testosterone therapy is to improve the sense of well-being, muscular strength and sexual function. Testosterone replacement therapy is also beneficial for the sexual parameters. It is believed that sudden testosterone withdrawal results in rebound effect i.e., increased sperm and GTs concentration (Liu and David 2003; Hamada et al. 2012). However, published data contraindicates, testosterone use, as a treatment choice for infertility. Astonishingly, even then American Urologic Association (AUA) has reported that 25% urologists still prescribe androgens for infertility (Li 2014).

Antioxidants

To reduce the level of oxidative stress in an infertile male different antioxidants are used, that improve fertility by decreasing the production of ROS. Several studies have reported that antioxidant supplementation treats oxidative stress induced male infertility (Ross et al. 2010). Following antioxidants are effective against the oxidative stress induced infertility in male.

Enzymatic antioxidants

Glutathione peroxidase (GP_x): Glutathione is an antioxidant which can enhance the sperm motility and especially the percentage of forward motility (Lenzi et al. 1993). GP_x is a significant agent in seminal enzymatic antioxidant pathway. It causes hydroperoxides reduction by glutathione. GP_x is located in seminal vesicles, vas deferens, testis, prostate, spermatozoa, seminal plasma and epididymis (Vernet et al. 2004). It combats oxidative attack, as its particular inhibition by mercaptosuccinate results in enhanced sperm lipid peroxidation (Dabaja and Schlegel 2014).

Superoxide dismutase (SOD) and Catalase: SOD inhibits lipid peroxidation in plasma membrane by catalyzing superoxide into H_2O_2 and oxygen and thus increases sperm motility. It conjugates with GP_x and catalase to convert H_2O_2into oxygen and H_2O. Both catalase and SOD counters ROS and prevents it from damaging the sperm (Agarwal et al. 2014).

Non-enzymatic antioxidants Vitamin C: Vitamin C is found in the human seminal plasma, where it protects the spermatozoa against endogenous damage from ROS (Colagar and Marzony 2009; Jung and Ju 2014). When vitamin C is given to some patients it expresses dose dependent result on sperms quality. When 1000 mcg of vitamin C is administered orally it may enhance the sperm motility while high dose of this vitamin may cause damage to sperm and can decrease sperm motility (Akmal et al. 2006). Table 4 represents dietary sources of vitamin C (Garcia-Closas et al. 2004).

Vitamin E (α-tocopherol): It a lipid soluble vitamin. Various studies (De Lamirande and Gagnon 1992) have reported that vitamin E enhance the performance of sperms by increasing sperm motility. It increases motility of sperm by decreasing the level of malondialdehyde to normospermic level (Suleiman et al. 1996). Table 4 represents dietary sources of vitamin E (Garcia-Closas et al. 2004).

Carnitines: Carnitine is an antioxidant which increases fertility by increasing sperm energy metabolism and boosting sperms motility (Jung and Ju 2014). Inside mitochondria, carnitine facilitated the transportation and utilization of free fatty acids. It also decreases fatty acid oxidation by restoring the phospholipids composition of mitochondrial membrane. Carnitine provides energy to spermatozoa; it is directly involved in maturation and motility of sperms (Sharma and Black 2009). Inside the mitochondria, low level of carnitine can reduce the concentration of fatty acid which in turn decreases the energy production and sperm motility (Sheikh et al. 2007). Table 4 represents dietary sources of Se (Oostindjer et al. 2014).

Selenium (Se**):** Se plays a vital rolein normal spermatogenesis, testicular development and sperm motility (Moslemi and Tavanbakhsh 2011). It protects DNA of sperm from oxidative damage. Some studies have also demonstrated the correlation between sperm concentration and seminal plasma Se concentration (Atig et al. 2012; Agarwal et al. 2014). Table 4 represents dietary sources of Se (Lemire et al. 2011).

Co-enzyme Q10 (CoQ-10): It is endogenously found inside the sperm. It is highly active in testis and ubiquinol, reduced CoQ-10is abundantly found in spermatozoa. Decreased levels of both CoQ-10 andubiquinol in spermatozoa and seminal plasma are found in idiopathic infertile males and asthenospermia (Talevi et al. 2013). Oral administration of CoQ-10 recovers fertility by inhibiting the production of hydrogen peroxide inside seminal fluid and improving sperm motility (Lafuente et al. 2013). Table 4 represents dietary sources of CoQ-10 (Saini 2011).

Zinc (Zn): It is also essential for normal functioning of male reproductive system (Jung and Ju 2014). It has a significant role in normal sperm motility and production of adequate semen concentration. Its concentration is higher in seminal plasma as compared to other tissues, where it stabilizes cell membrane and spermchromatin (Atig et al. 2012). Deficiency of Zn in males can decrease the level of testosterone and sperm count (Dissanayake et al. 2009). Table 4 represents dietary sources of Zn (Solomons 2001).

Table 4 Dietary sources of non-enzymatic antioxidants

Vitamin C	Vitamin E	Carnitine	Selenium	CoQ-10	Zinc
Cabbage	Nuts & seeds	Beef	Oat	Fish (salmon/tuna)	Meat
Broccoli	Seed oil	Pork	Garlic	Organ meats (liver)	Fish
Citrus fruits	Wheat germ	Lamb	Onion	Whole grains	Chicken
Red pepper	Eggs	Dairy products	Brown rice		Eggs
Melon	Whole grains		Barley		Pumpkins
Mango			Whole grains		Beans
Spinach					Rye
Papaya					Oat
					Pulses

Anti-inflammatory therapy

Corticosteroids Anti-sperm antibodies restrict sperm function and motility, thereby decreasing possibility of pregnancy. In that case corticosteroids are used as specific treatment for antibodies associated male infertility (Hamada et al. 2013). There is no standardized treatment available for immunologic infertility in men, but oral corticosteroids e.g. prednisolone can suppress the production of antibodies effectively (Kamischke and Nieschlag 1999).

Non-steroidal anti-inflammatory drugs (NSAIDs) Leukocytes have negative effect on sperm (Jung and Ju 2014). In infertile males they are commonly found in seminal plasma. It has been reported that rofecoxib (COX-2 inhibitor) considerably reduces leukocytospermia and upgrades sperm parameters (morphology, concentration and motility) (Wolff 1995; Hamada et al. 2013).

Antibiotics

Some GTI_s increase white blood cell level and can cause leukocytospermia, which is found to be associated to decrease sperm motility and male fertility (Berger et al. 1982; Maruyama et al. 1985). Antibiotic therapy can be used against these infections. Doxycycline, tetracycline, fluoroquinolones, norfloxacin, levofloxacin, ciprofloxacin, macrolide and erythromycin are mainly used to treat the identified GTI_s (Haidl and Schill 1991).

Alpha-adrenergic agonists

For the treatment of ReE alpha-adrenergic agonists such as imipramine, ephedrine and pseudoephedrine are commonly used (Jung and Ju 2014). These drugs cause ejaculation by increasing the sympathetic tone of vas deferens and internal sphincter. Continuous administration of these drugs can develop tolerance (Hendry et al. 1990). However, the therapy is used with little success due to AnE (Hamada et al. 2013).

Non-pharmacological treatment (surgical treatment)

Treatment of obstructive and non-obstructive infertility includes surgical involvement. In non-obstructive infertility, surgical sperm retrieval is mandatory for effective treatment with intracytoplasmic sperm injection (ICSI). There is 100% retrieval rate of sperm in obstructive infertility in surgical treatment. Typical surgical treatment is cost effective than alternative forms of treatment like assisted reproduction procedures (ART) (Seo et al. 2010; Cho and Seo 2014).

Assisted reproductive technologies (ART)

Male infertility can be managed by ART. These include laboratory techniques in which there is manipulation of male and female gametes for reproduction. These include ICSI, in vitro fertilization (IVF) and Intra-uterine insemination (IUI) (Sabarre et al. 2013). Most ART centers use ICSI as priority option for infertility. In ICSI, oocytes in metaphase-II phase are prepared by removal of corona radiata and cumulus mass with hyaluronidase. Then one sperm from epididymis, ejaculate or testis is injected by a micropipette into oocyte cytoplasm, which has already been immobilized under oil. During injection the cytoplasm is aspirated and injected, to activate oocyte and improve fertilization. As spermatozoa influences oocyte activation, spermatozoa immobilization is persuaded via distorting sperm tail between injection micropipette and Petri dish bottom (Khorram et al. 2001). IVF with ICSI (IVF/ICSI) also allows couples to become fertile. Literature has published offspring safety of IVF/ICSI. However, more study is required to determine risks associated with ART offsprings (Alukal and Dolores 2008).

Varicocelectomy

Various techniques are available for varicocele treatment. These are divided into two types: surgical and radiological method (Inci and Gunay 2013). Surgical techniques are classified in to microsurgical, laparoscopic and conventional open methods. Meanwhile, others areinguinal, retroperitoneal, scrotal and subinguinal approaches according to access level. Radiological treatment is alternativelyused with less invasiveness and significance to control small collaterals which are not detected while surgery (Cho and Seo 2014; Binsaleh and Lo 2007). Laparoscopic varicocelectomy is an effective technique for the disease. Robotic surgery is another varicocelectomy option that has recently introduced (Chan 2012). However, microsurgical varicocelectomy is more reputed procedure among surgeons and is considered a gold standard owing to itsgreater surgical outcomes (Chan 2012; Cho and Seo 2014).

Vasoepididymostomy (VE)

OI can be treated by microsurgical reconstruction along with VE (Baker and Sabanegh 2013; Wosnitzer et al. 2014). Microsurgical VE is a challenging microsurgery as its success level depends on experience and skills of the surgeon. There are numerous techniques for VE. However, in longitudinal intussusception VE (LVE) there is longitudinal opening of epididymal tubule to get a bigger opening to permit passage of its tubular content via the anastomosis (Chan 2013; Jungwirth et al. 2012).

Table 5 Plants used to treat male infertility

S. No.	Botanical name of the plant	Family	Parts used	Effects	References
1	*Aframomum melegueta*	Zingiberaceae	Fruits	Improve sexual behavior	Kamtchouing et al. 2002.
2	*Acanthopanacis senticosi*	Araliaceae	Whole plant (aqueous extracts)	Increase sperm motility	Liu et al. 2004; Mkrtchyan et al. 2005
3	*Alpinia calcarata Roscoe*	Zingiberaceae	Rhizomes	Increase level of testosterone and sexual behavior	Ratnasooriya and Jayakody, 2006
4	*Aspidosperma ulei markgr*	Apocyanaceae	Root	Increase penile erection	Campos et al. 2006
5	*Astragalus membranaceus*	Fabaceae	Root	Increase sperm motility	Liu et al. 2004; Kim et al. 2016
6	*Basella alba L.*	Basellaceae	Leaves	Increase blood testosterone level	Ramachandran et al. 2004
7	*Butea frondonsa*	Fabaceae	Bark	Increase ejaculation	Ramachandran et al. 2004
8	*Casimiroa edulis la llave*	Rutaceae	Seed	Improve sexual activity	Ali and Rakkah 2008
9	*Catha edulis Forsk*	Celastraceae	Leaves	Enhancing sexual motivation/arousal	Abdulwaheb et al. 2007; Wabe, 2011
10	*Cocculus hirsutus Linn.*	Menispermaceae	Aerial part	Spermatogenic	Sangameswaran and Jayakar 2007.
11	*Croton zambesicus*	Euphorbiaceae	Leaves	Increase sperm number and motility	Ofusori et al. 2007
12	*Cynomorium coccineum L.*	Cynomoraceae	Roots	Increase sperm count and increase spermatogenesis	Abd El-Rahman et al. 1999.
13	*Dactylorhiza hatagirea*	Orchidaceae	Seeds	Increase testosterone level	Thakur and Dixit 2007
14	*Dracaena arborea*	*Asparagaceae*	Root bark	Increased erection	Watcho et al. 2007; Wankeu-Nya et al. 2013
15	*Epimedium koreanum Nakai*	Berberidaceae	Herbs	Improves sexual activity	Ang et al. 2001
16	*Eurycoma longifolia*	*Simaroubaceae*	Roots	Stimulate sexual arousal	Ang et al. 2001; Kotta et al. 2013
17	*Garcinia cambogia Desr.*	Clusiaceae	Seeds	Increase sperm count	Oluyemi et al. 2007.
18	*Ginkgo biloba*	*Ginkgoaceae*	Leaves	Increase ejaculatory frequency	Yeh et al. 2008; Oshio et al. 2015
19	*Hibiscus sabdariffa L.*	Malvaceae	Flowers	Increase Sperm count	Amin and Hamza 2006
20	*Lepidium meyenii Walpers*	Brassicaceae	Root	Spermatogenesis	Zheng et al. 2000
21	*Montanoa tomentosa*	Asteraceae	Leaves and flowers	Stimulate sexual arousal	Carro-Juarez et al. 2004; Kotta et al. 2013
22	*Mucuna pruriens*	Fabaceae	Seed	Spermatogenic	Shukla et al. 2007
23	*Panax ginseng*	Araliaceae	Root	increased physical strength	Murphy et al. 1998; Kotta et al. 2013
24	*Peganum harmala L.*	Zygophyllaceae	Seed	Spermatogenesis and increase organ weight	Hamden et al. 2008
25	*Pentadiplandra brazzeana Baill*	Capparidaceae	Root	Increases serum and testicular testosterone levels	Kamtchouing et al. 2002.
26	*Pfaffia paniculata*	Amaranthaceae	Root	Stimulates ejaculatory performances	Arletti et al. 1999
27	*Phoenix dactylifera*	Arecaceae	Pollen	Improve sperm count, motility, morphology and DNA quality	Bahmanpour et al. 2006; Kotta et al. 2013
28	*Psidium guajava Linn*	Myrtaceae	Leaves	Increases sperm count	Akinola et al. 2007.
29	*Psoralea corylifolia L.*	Fabaceae	Fruits	Spermatogenesis and increases sperm count	Yang et al. 2008.
30	*Rubus coreanus Miq*	Rosaceae	Fruit	Increase spermatogenesis	Oh et al. 2007.
31	*Semen cuscutae*	Convolvulaceae	Seeds	Increase sperm motility	Qin et al. 2000; Zhang et al. 2003

Table 5 (continued)

S. No.	Botanical name of the plant	Family	Parts used	Effects	References
32	*Senecio cardiophyllus Hemsl*	Asteraceae	Root	Increase ejaculatory capacity	Carro-Juarez et al. 2009
33	*Terminalia catappa*	*Combretaceae*	Seed	Increase sexual vigor	Ratnasooriya and Dharmasiri 2000
34	*Tribulus alatus Delile*	Zygophyllaceae	Aerial parts and fruits	Increase serum testosterone	El-Tantawy et al. 2007.
35	*Tribulus terrestris L.*	Zygophyllaceae	Fruits	Increase androgen level	Gauthaman et al., 2002
36	*Trichopus zeylanicus*	Trichopodaceae	Leaves	increased mating performances	Subramoniam et al. 1997
37	*Turnera diffusa*	*Turneraceae*	Leaves and other aerial parts	Stimulates ejaculatory performances	Arletti et al. 1999; Kotta et al., 2013
38	*Vanda tessellata*	Orchidaceae	Roots, flowers, leaves	Increasemating performances	Kumar et al. 2000
39	*Zingiber officinale Roscoe*	Zingiberaceae	Roots	Increase serum testosterone levels	Kamtchouing et al. 2002
40	*Withania somnifera*	Solanaceae	Root	Increase semen volume, sperm count and motility	Devi et al. 2004; Ambiye et al. 2013

Vasovasostomy (VV)

About 3–6% vasectomised males request VV to regain fertility (Elzanaty and Dohle 2013; Herrel and Hsiao 2013; Wespes 2014). During VV it is mandatory to ensure sufficient supply of blood to anastomosis. In VV, watertight anastomosis is essential to avoid formation of secondary scar. Microdot method of VV allows precise gathering of markedly discrepant lumens. Thereby, there is separation of planning from suture placement that prevents dog-ears besides subsequent leaks (Herrel and Hsiao 2013). Microsurgical VV is a standard reversal procedure. However, it is challenging to surgeons and time-consuming. Therefore, other vasal anastomosis procedures like robotic-assisted VV are preferred (Elzanaty and Dohle 2013; Wespes 2014).

Microsurgical epididymal sperm aspiration/testicular sperm extraction (MESA/TESE)

MESA/TESE is implemented with ICSI when it's not likely to perform VV. Testicular biopsy is performed if MESA is unable to produces permatozoa or produce a very small spermatozoa count (Jungwirth et al. 2012). In MESA there is no suturing or microsurgical dissection. It is a quick process, which do not require special training or equipment and is carried out by using local anesthesia. In obstructive infertility patients, sperm can be retrieved from testis or epididymis while in non-obstructive infertility, TESE is the only useful technique (Shah 2011). TESE is executed on different locations of testes. It is the only choice for spermatozoa retrieval in NOI due to testicular dysfunction (Jungwirth et al. 2012).

Combination therapy

Combinations of hormones and hormones plus anti-oxidants are used as an empirical therapy for idiopathic male infertility (Jung and Ju 2014). Tamoxifen plus testosterone significantly increases testicular volume and sperm motility and concentration (Hamada et al. 2013). Similarly, clomiphen plus vitamin E also increase pregnancy rate and sperm concentration (Ghanem et al. 2010).

Ethno-pharmacological treatment

Medicinal plants treat male infertility empirically as decoctions, extracts, fractions and semi-purified compositions. These products treat; sperm, erection and libido dysfunctions. Various studies have reported pharmacological properties of different plants in vitro on cell lines and in vivo in animals (Table 5) (Nantia et al. 2009). However, due to lack of established clinical parameters physicians and patients are reluctant to their usage. There is requirement of clinical trials to explore molecular and cellular mechanism

of these medicinal plants. Research on validation of these plants will expose a new approach in treating male infertility (Chauhan et al. 2014).

Conclusion

Male infertility drastically affects a couple's social and psychological behavior. Therefore, it is essential to recover patient's reproductive health. There are different social, genetic and environmental factors that cause male infertility. Urologists take case history and execute physical examination for initial screening. Semen analysis is a first line diagnostic parameter for determining the cause of infertility. Pharmacologic treatment is effective only when etiology of infertility in known. Based on literature, hormonal treatment is generally not used extensively for treating idiopathic infertility because of doubtful efficacy. In case of treatment failure and idiopathy, patients are recommended to try assisted reproductive technologies. In non-obstructive infertility, testicular sperm extraction followed by intracytoplasmic sperm injection is advised. Researchers have explored pharmacological properties of different medicinal plants against male infertility. However, they are not recommended by physician due to inadequate clinical data on their safety, efficacy and adverse effects.

Acknowledgments We are grateful for all the help provided by Dr. Talha Jawaid, Assistant Professor, Dar Al Uloom University, Riyadh, Kingdom of Saudi Arabia.

Compliance with ethical standards

Conflict of Interest The authors report no declaration of interest.

Ethical statement N/A

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