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INVITED REVIEW

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The physiology of male reproduction: Impact of drugs and their abuse on male fertility

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Abstract

Male factor accounts for about 30–50% of infertility. A common cause of male infertility is drug abuse; either illicit or prolonged use of prescribed drugs. This study provides a review of the physiology of the hypothalamic–pituitary–gonadal axis and recent literature on drugs that have been linked to male infertility and the associated mechanisms. Relevant peer-reviewed papers were assessed online using PubMed/PubMed Central, Scopus, AJOL, Google Scholar and DOAJ databases using Medical Subjects Headings (MeSH) indexes and relevant key word searches. Although drugs are beneficial when used at therapeutic levels, the abuse leads to impairment of hypothalamic–pituitary–gonadal functions, increased sperm DNA fragmentation and apoptosis, and reduced sperm quality. A good knowledge of the physiology of the hypothalamic–pituitary–gonadal axis and the influence of drugs on male fertility will guide healthcare providers in managing cases of infertility.

KEYWORDS

FSH, infertility, LH, oestrogen receptors, testes

1 | INTRODUCTION

Infertility is the failure of a couple to achieve conception after 12 months of adequate unprotected sexual intercourse (Wiwanitkit, 2008). It is a major health challenge with social implications among couples, particularly in the tropics (Yeşilli et al., 2005). Although Mascarenhas, Cheung, Mathers, and Stevens (2012) suggested a dearth of data on the global prevalence of infertility, Boivin, Bunting, Collins, and Nygren (2007) documented that about 72.4 million couples experience fertility problems globally. This accounts for about 15% of couples (Dissanayake, Keerthirathna, & Peiris, 2019). Contrary to the popular misconception that infertility is attributable to female factor, it has been established that about 30%–50% cases of primary infertility is due to male factor (Ajayi & Akhigbe, 2017; Fronczak, Kim, & Barqawi, 2012; Yeşilli et al., 2005). Common causes of male infertility include genetic disorder, endocrinopathies, immunological disorders and sperm antibodies, testicular pathologies, obstruction of the reproductive tract, systemic disorders and inflammatory conditions such as epididymo-orchitis (Bonde 1996; Ajayi & Akhigbe, 2017). Drugs, prescribed and non-prescribed, have also been implicated in the aetiopathogenesis of reproductive dysfunction (Bonde 1996). The rise in substance abuse could account for increasing prevalence of infertility, possibly via its influence on the hypothalamic–pituitary–testicular axis.

This review highlights the functions of the hypothalamic–pituitary–testicular axis and factors that modify this axis with emphasis on common drugs that have been reported to adversely affect male reproduction. Our aim is to provide a useful tool for healthcare givers involved in the management of male infertility. It also opens new grounds to be explored by researchers. The present study reviewed all available data published in peer-reviewed journals up to date. A systematic search was made through the PubMed/PubMed Central, Scopus, AJOL, Google Scholar and DOAJ databases using Medical Subjects Headings (MeSH) indexes and relevant key word searches. Papers that did not adequately discus details of the study were excluded. Duplicated records were also excluded.

2 | HYPOTHALAMIC–PITUITARY–GONADAL/TESTICULAR AXIS

The reproductive system is regulated by the hypothalamic–pituitary–gonadal axis (Ajayi, Akhigbe, & Ajayi, 2013) (Figure 1). The hypothalamus is located at the base of the brain, on the floor of the third ventricle, superior to the optic chiasm and pituitary gland, and inferior to the thalamus (Sheng and Westphal, 1999). It produces 'releasing hormones', also known as 'hypothalamic hormones' (Corradi, Corradi, & Greene, 2016). The releasing hormones regulate the secretion of the pituitary hormones. The pituitary stalk is the neurovascular connection between the hypothalamus and the pituitary gland (Sheng and Westphal, 1999; Corradi et al., 2016).

The pituitary gland is also called the hypophysis (Corradi et al., 2016). It lies in the sella turcica, a depression in the skull inferior to the hypothalamus (Sheng and Westphal, 1999). It is ectodermal in origin and made up of two physiologically different structures that vary embrologically and anatomically: the adenohypophysis (anterior pituitary) and neurohypophysis (posterior pituitary) (Sheng and Westphal, 1999; Corradi et al., 2016). 'The adenohypophysis develops from an upward invagination of the oral ectoderm called Rathke's pouch, while the neurohypophysis is from the downward extension of the neural ectoderm, the infundibulum' (Sheng and Westphal, 1999).

Co-ordination of the hypothalamic–pituitary–testicular axis is necessary for the normal physiological function of the testes (Corradi et al., 2016). It influences testosterone synthesis and male reproductive function. The pulsatile secretion of gonadotropin-releasing hormones (GnRH) by the hypothalamus triggers the synthesis of the pituitary gonadotropins, luteinising hormones (LH) and follicle stimulating hormone (FSH), which maintains intra-testicular production of testosterone and spermatogenesis (Corradi et al., 2016). The hypothalamic–pituitary–testicular axis is controlled by feedback mechanisms. Sufficient level of testosterone leads to a decrease in the secretions of GnRH, FSH and LH via a negative feedback control (Corradi et al., 2016; Dhillo, Chaudhri, & Patterson, 2005) (Figure 1).

GnRH is a decapeptide that binds to membrane receptors on the pituitary gonadotrophs, triggering the secretions of the gonadotropins (Corradi et al., 2016; Dhillo et al., 2005). Experimental studies observed that pre-treatment with GnRH in GnRH-deficient mice induced a rise in FSH and LH (Young, Speight, & Charlton, 1983) as well as an increase in GnRH receptors expression in the pituitary gland (Charlton, Halpin, & Iddon, 1983). The number of GnRH receptors differs and directly correlates with the capacity of pituitary gonadotrophs to secrete gonadotropins (Corradi et al., 2016). Also, the pulsatile secretion of GnRH is required for pituitary gonadotropin signalling (Corradi et al., 2016; Santen & Bardin, 1973). This pulsatility is a calcium-dependent intrinsic function of the hypothalamic cells (Wetsel, Valencia, & Merchenthaler, 1992). Findings from a study in GnRH-deficient mice following GnRH administration observed an immediate and continuous rise in the plasma levels of FSH. On the other hand, LH secretion required a more persistent and pulsatile GnRH administration (Corradi et al., 2016; Marshall, 1985).

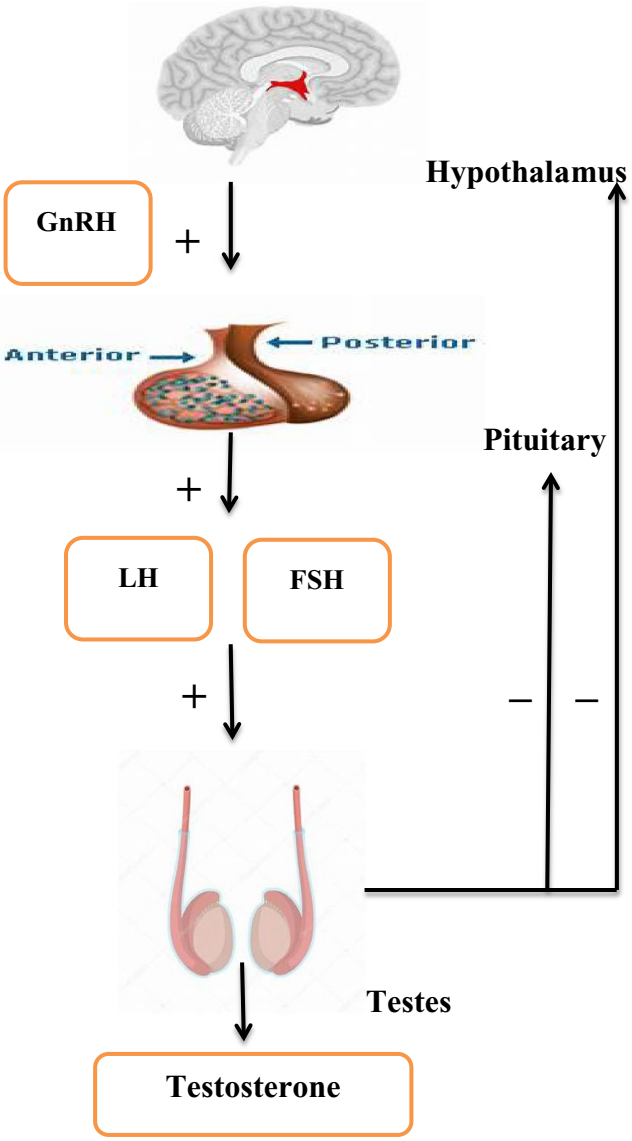

FIGURE 1 The hypothalamic–pituitary–testicular axis. Luteinizing hormone releasing hormone (LHRH) from the hypothalamus stimulates the pituitary gland to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In males, LH stimulates testosterone production and FSH is important to sperm maturation. +, stimulatory effect; –, inhibitory effect.

This implies that FSH is continuously synthesised even in the absence of persistent GnRH stimulation, but sustained stimulation of GnRH is necessary for the synthesis of LH.

2.1 | Follicular stimulating hormone, luteinising hormone, and testicular function

Follicular stimulating hormone and LH are similar in structure. They are made up of α and β peptide chain subunits that are synthesised in the pituitary gland (Corradi et al., 2016; Trarbach, Silveira, & Latronico, 2007). Although the α subunit is similar in both gonadotropins, the β subunit differs. Hence, the specificity of the hormones

for receptor binding and their biological actions is dependent on the β subunit (Corradi et al., 2016).

Follicular stimulating hormone determines the population of testicular Sertoli cells, and the induction and maintenance of spermatogenesis (Wetsel et al., 1992). Luteinising hormone triggers the release of gonadal steroids via Leydig cell activity (O'Shaughnessy, Monteiro, & Verhoeven, 2010; Wetsel et al., 1992). FSH triggers a rise in cyclic adenosine monophosphate, thus stimulating a cyclic adenosine monophosphate-dependent protein kinase (O'Shaughnessy et al., 2010). This increases androgen-binding protein (sex hormone-binding globulin [SHBG]) and the aromatase enzyme CYP19 biosynthesis, which converts testosterone to oestradiol (Means, Fakunding, & Huckins, 1976; O'Shaughnessy et al., 2010).

Steroidogenesis is controlled by LH which acts via specific receptors located on the testicular leydig cells and induces the conversion of cholesterol to testosterone (Handelsman, 2006). Leydig cell secretion causes a rise in the concentration of testosterone within the testis (Handelsman, 2006; Louise, Blount, & Leal, 2004). With sufficient concentrations of testosterone, the biosynthesis and release of pituitary LH and FSH declines through a negative feedback mechanism. There is also associated fall in GnRH release, thus reducing testosterone concentrations (Handelsman, 2006; Louise et al., 2004). Most of the negative feedback regarding FSH occurs through inhibins and activins. These are testicular peptide hormones and members of the transforming growth factor-β super family of molecules (Louise et al., 2004). Although inhibin B is more important, both inhibins A and B are produced by the Sertoli cells. Inhibins suppress FSH secretion, thus influencing FSH stimulation by activins (Louise et al., 2004). Follistatins, which are synthesised in the pituitary, bind activins and suppress their function (Handelsman, 2006; Louise et al., 2004). Inhibins also act within the testes as paracrine hormones (Louise et al., 2004).

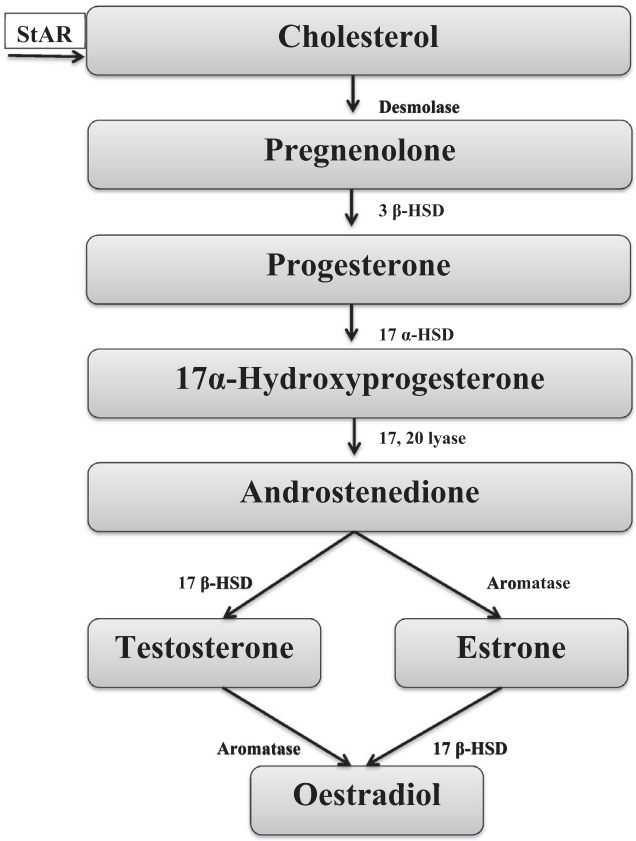

FIGURE 2 Biosynthesis of testosterone. StAR transport cholesterol to the inner mitochondrial membrane for desmolase action. This is the rate-limiting step in Steroidogenesis. Desmolase is located in the mitochondria, while other enzymes involved in androgen synthesis are located in the smooth endoplasmic reticulum. All enzymes involved in androgen synthesis are P450 enzymes except 3 β-HSD and 17 β-HSD. StAR, steroidogenic acute regulatory protein; HSD, hydroxysteroid dehydrogenase

2.2 | Peripheral metabolism of testosterone

Only about 5% of the circulating testosterone in post-pubertal age is from the adrenal gland; majority is from the testes. Testosterone is either protein-bound (98%) or free hormone (2%). 'Protein-bound testosterone either binds to low-affinity, high-availability proteins (primarily albumin) or to the high-affinity, low-abundance SHBG, a glycoprotein (Corradi et al., 2016)'. The free unbound form is the biologically active form of testosterone. Testosterone at the peripheral sites is converted to other steroids with different biological activities. (Figures 2 and 3) (Corradi et al., 2016). Although just a small amount of serum testosterone (5%) is reduced to dihydrotestosterone (DHT) by 5α-reductase, this metabolite is very potent and accounts for most of the important biological activities of testosterone (Russel & Wilson, 1994). Interestingly, both androgens share the same receptor. The affinity of DHT to androgen receptor is about 2–3 times more than that of testosterone (Corradi et al., 2016; Grino, Griffin, & Wilson, 1990; Russel & Wilson, 1994). Testosterone also dissociates five times faster than DHT from the androgen receptor (Grino et al., 1990). In addition, DHT cannot be converted to oestrogen (Grino et al., 1990).

During embryogenesis, DHT is essential for male external genitalia development, while in adult, it plays a prominent role in the physiological functions of the hair follicles and prostate (Amory, Anawalt, Matsumoto, 2008). Deficient 5α-reductase is linked to low conversion of testosterone to DHT and consequent insufficient level of DHT. This results in male infant with feminine appearance and a small phallus and internal testes (Kang, Imperato-McGinley, & Zhu, 2014). However, after puberty, under the influence of high testosterone concentrations, the penis enlarges and the male appearance evolves (Amory, Anawalt, & Matsumoto, 2008; Kang et al., 2014). In adult, the prostate gland enlarges and the characteristic male pattern hair loss ensues following the formation of DHT from testosterone (Kang et al., 2014; Zhu & Imperato-McGinley, 2009). With the understanding of this mechanism, 5α-reductase antagonists like finasteride are used to reduce the size of prostate in benign prostatic hypertrophy (BPH) and to prevent male balding (Zhu & Imperato-McGinley, 2009). However, this drug has been shown to impair phallus development

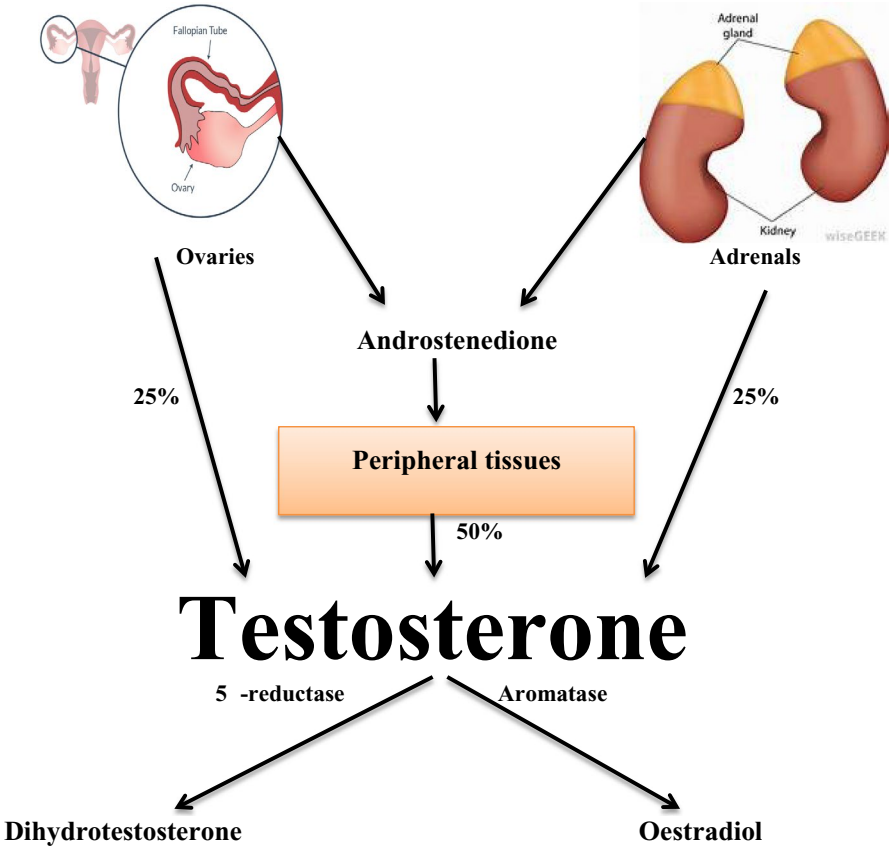

FIGURE 3 Peripheral metabolism of testosterone

in male foetus when used by pregnant women (Corradi et al., 2016; Kang et al., 2014; Zhu & Imperato-McGinley, 2009).

In peripheral tissues, under the influence of microsomal P450 enzyme CYP19 aromatase which is present in the gonads and some other sites like the brain, placenta and fat, testosterone can be converted to oestrogens (Longcope, Kato, & Horton, 1969; Corradi et al., 2016). Greater than 80% of serum oestradiol in men is from the aromatisation of testosterone (Leder, LeBlanc, & Schoenfeld, 2003); hence, male hypogonadism is strongly associated with hypo-oestrogenism (Corradi et al., 2016; Leder et al., 2003). When there is deficient aromatisation of testosterone to oestrogen, there is a raised level of testosterone and a low level of oestrogen. The low level of oestrogen causes increased levels of LH (Finkelstein, Lee, & Burnett-Bowie, 2013). This reveals that low level of oestrogen rather than testosterone level is more important feedback to the pituitary. Oestrogen also plays vital role in bone metabolism, body fat regulation and male sexual function (Finkelstein et al., 2013). In obesity and insulin resistance, high adiposity is linked with increased conversion of testosterone to oestrogen by aromatase in fat tissue, usually leading to lower levels of testosterone and gynaecomastia (Corradi et al., 2016; Finkelstein et al., 2013).

2.3 | Sexual development in males

Although variations exist in the hypothalamic GnRH-stimulated gonadotropin secretion during sexual development, pulsatile secretion of GnRH is essential to maintain reproductive function (Corradi et al., 2016). The reproductive axis is associated with neuroendocrine stimulation during foetal development (Corradi et al., 2016; Leder et al., 2003). Despite that GnRH neurons appear earlier in foetal life, the link between the portal system of the hypothalamus and pituitary, and these GnRH neurons only become functional at about the 16th week of gestation (Achermann & Jameson, 1999; Waldhauser, Weibenbacher, & Frisch, 1981). Although these neurons are functional at birth, they are suppressed tonically at infancy after the perinatal androgen surge (Corradi et al., 2016). In early life, there is low pulse frequency and low amplitude GnRH secretion at the hypothalamic–pituitary axis (Corradi et al., 2016; Leder et al., 2003). Although the main neuroendocrine trigger of puberty is yet unclear, the onset is characterised by sleep-entrained reactivation of the reproductive axis associated with significant rise in the amplitude, but minimal variation in frequency of LH pulses (Leder et al., 2003; Waldhauser et al., 1981).

Initially, gonadal secretion of sex steroids is stimulated by elevation of LH secretion at night which returns to prepubertal concentrations at daytime (Leder et al., 2003). However, gonadotropin secretions occur during day and night as puberty progresses (Achermann & Jameson, 1999; Boyar, Rosenfeld, & Kapen, 1974; Leder et al., 2003). This ensures the attainment of full sexual development. The testicular production of testosterone overrides the hypothalamic GnRH release, hence ensuring a persistent frequency of LH pulses, and the sleep-entrained LH and testosterone fluctuations become inconsequential (Achermann & Jameson, 1999; Corradi et al., 2016). The increased levels of testosterone and the DHT at this time account for voice deepening, secondary sex hair

distribution, growth of the penis and testicles, and increased libido (Corradi et al., 2016). Higher concentrations of testosterone and its conversion to oestrogen explains the development of muscle mass, bone maturation and accelerated bone growth seen until closure of the epiphyses of long bones. During adulthood, pulsatile GnRH continues to trigger LH and FSH production which maintains testicular biosynthesis of testosterone and spermatogenesis as well as systemic production of testosterone and virilisation (Boyar et al., 1974; Corradi et al., 2016).

2.4 | Sex Steroid receptor

Mutations of androgen receptor can affect fertility either by impairing the action of testosterone and DHT in the testes or influencing the synthesis of gonadotropin. About 200 mutations of androgen receptor have been documented (Achermann & Jameson, 1999). Milder forms of androgen insensitivity may manifest as infertility. Most times, this is due to missense mutations in the ligand-binding domain (Achermann & Jameson, 1999; Phillip, Arbelle, Segev, & Parvari, 1998). Hence, the androgen receptor is a risk factor for idiopathic infertility (Achermann & Jameson, 1999). Contrary to this, just a human oestrogen receptor (α) mutation has been reported in males, but none in females (Lindstedt et al., 1998; Phillip et al., 1998). This oestrogen receptor mutation was associated with normal pubertal development, normal sperm concentration, but low sperm viability (Lindstedt et al., 1998; Phillip et al., 1998).

Oestrogen receptors also play key roles in male fertility. Selective oestrogen receptor modulators (SERMs) act as either oestrogen agonists or antagonists in a tissue-specific manner (Plouffe & Siddhanti, 2001). At the level of the hypothalamus–pituitary, these modulators block oestrogen receptors, hence stimulating GnRH secretion and consequently gonadotropin secretion (Kumar et al., 2006; Cocuzza & Agarwal, 2007). The rise in gonadotropins enhances spermatogenesis and possibly androgen production.

In a meta-analysis report, Cannarella et al. (2019) reviewed studies that documented the effect of SERMs, such as clomiphene citrate, tamoxifen, toremifen and raloxifene, on male reproduction and fertility indices. It was documented that SERMs significantly increased sperm concentration and count, as well as enhanced sperm morphology. Selective oestrogen receptor modulators were also reported to markedly increase serum levels of FSH, LH and testosterone. Interestingly, SERMs also significantly increased pregnancy rate. The beneficial effect of SERMs on male reproduction is via several mechanisms. Selective oestrogen receptor modulators interfere with the negative feedback that normally regulates GnRH release and thus indirectly induce pituitary secretion of gonadotropins with resultant stimulation of spermatogenesis (Kumar et al., 2006; Cocuzza & Agarwal, 2007). In addition, they possibly improve Leydig cell sensitivity to LH, thus stimulating testosterone synthesis (Cannarella et al., 2019). They have also been reported to interfere with xenoestrogens which are usually found in high concentrations in the semen of infertile patients (Vandekerckhove, Lilford, & Vail, 2000). SERMs may also stimulate sex hormone binding globulin (SHBG) secretion from hepatocytes via their oestrogenic activities (Riggs & Hartmann, 2003; Rozati, Reddy, & Reddanna, 2002). Surprisingly, SERMs have been demonstrated to have antioxidant properties. Tamoxifen has been observed to increase seminal total antioxidant capacity and reduce sperm ROS and MDA (Guo, Jing, & Feng, 2015). It also increases sperm succinate dehydrogenase activity, mitochondrial membrane potential and adenosine triphosphate levels (Nada, El Taieb, & Ibrahim, 2015).

Oestrogen receptor mutations and polymorphisms have also been implicated in the aetiopathogenesis of male infertility. Aschim, Giwercman, Ståhl, and Eberhard (2005) reported a strong association between genetic variants of *ERβ* gene and male infertility. They observed that the frequency of *RsaI* AG genotype of *ERβ* was higher in infertile men than in their control counterpart. Bordin and Moura (2015) also reported that *RsaI* AG genotype of the gene for *ERβ* in men with azoospermia, oligozoospermia, asthenozoospermia or teratozoopermia is approximately four times higher than in men with normospermia. Although the mechanism associated with this polymorphism and infertility is still poorly understood, it is speculated that the polymorphism is in disequilibrium with other genetic variations that may affect gene expression and/or function (Aschim et al., 2005).

Ge et al. (2014) summarised the differential association of polymorphisms in oestrogen receptors (*PvuII*, *XbaI*, *RsaI and AluI*) with male infertility in their meta-analysis and systematic review. Overall, it was found that the *PvuII* polymorphism in *ESR1* was associated with significant decrease in the risk of male infertility. Although *ESR1 PvuII* polymorphism was significantly associated with a decreased risk of male infertility in Asian, it was associated with an increased risk of male infertility in Caucasians. Furthermore, no association was found between *XbaI* polymorphism in *ESR1* and male infertility. However, on stratification analysis by ethnicities, there was a significant association between *XbaI* polymorphism in *ESR1* and male infertility in Asian population, but none in the Caucasian population. In addition, *ESR2 RsaI* polymorphism was associated with a lower risk for male infertility in homozygote comparison and an increased risk in heterozygote comparison. On ethnic stratification, *ESR2 RsaI* polymorphism was significantly associated with a decreased infertility risk in the Asians and an increased risk in the Caucasians. It is noteworthy that *ESR2 AluI* polymorphism was observed not to be associated with male infertility even with further ethnic stratification. It can thus be inferred from the study of Ge et al. (2014) that polymorphisms of oestrogen receptor genes may have differential roles in the predisposition to male infertility according to the different ethnic background.

Meta-analysis of Li et al. (2014) documented the association between single nucleotide polymorphisms (SNPs) in oestrogen receptors and male infertility considering the four common SNPs: rs2234693, rs9340799, rs1256049 and rs4986938. It was observed that the

rs2234693C allele was associated with a decreased risk for male infertility; however, the rs9340799AA genotype and the rs1256049GA genotype were associated with an increased risk for male infertility.

2.5 | Other modifiers of hypothalamic–pituitary–testicular axis

The hypothalamic–pituitary–testicular axis is influenced by inhibin, activin and follistatin. A number of transgenic models involving these factors exhibit impaired male fertility (Achermann & Jameson, 1999). Inhibin is made up of one α-subunit and either of the two distinct β-subunits (βA and βB). It suppresses FSH (Latronico et al., 1998). Alteration of the α-subunit causes raised FSH and tumours of gonadal stromal. This is possibly due to unopposed activin actions (Achermann & Jameson, 1999). The influence of overexpression of inhibin on fertility is not clear, and its receptor has not been characterised (Guo et al., 1998). Activin is made up of dimers of the inhibin β-subunits (A, AB, B), and it triggers FSH. Alteration of β-A subunit is lethal while that of the β-B subunit influences female reproduction. Activin receptor type II (Act R II) deletion is strongly associated with impaired fertility. Overexpression of follistatin, an activin-binding protein, has been implicated in the pathophysiology of infertility (Achermann & Jameson, 1999; Guo et al., 1998; Latronico et al., 1998).

3 | DRUG ABUSE

Drug abuse is a major global public health challenge (United Nations Organizations on Drug Council (UNODC) 2005). Drug abuse by adolescents is a worrisome health-related issue globally (National Drug Law Enforcement Agency 1997). 'Drug abuse is the excessive and/persistent self-administration of a drug without regard to the medically or culturally accepted patterns' (Haladu, 2003). It is 'the use of a drug to the extent that it interferes with the health and social function of an individual' (Fareo, 2012). It can be defined as the nonmedical use of a particular drug that adversely affects a health. It was defined by Manbe (2008) as 'the excessive, maladaptive or addictive use of drugs for non-medical purpose'. It is seen as 'the use of drugs to the extent that they interfere with the health and social function of an individual' (Abdulahi, 2009). Summarily, drug abuse is an indiscriminate and inappropriate use of drug, either for medical or nonmedical purposes, at the expense of one's health.

According to the World Health Organization (World Health Organization (WHO) 2013) report, 320, 000 young people between 15 and 29 years of age die annually from alcohol-related drugs, resulting in 9% of all deaths. This report revealed that at least 15.3 million persons have drug use disorders. The prevalence and pattern of drug abuse varies across the globe. In the UK, Isaac and Holloway (2005) reported that 71.3% of the patients in the psychiatric intensive care unit abused cannabis. Barnett, Werners, and Secher (2007) observed that 51% of patients in the UK population abused cannabis, 43% abused alcohol, and 38% were reported to be involved with polysubstance. According to Cassidy et al. (2001), the rate of lifetime substance abuse was higher for both alcohol (48.5%) and drugs (43.9%). About 60% of the cohort had a history of substance abuse. In the United States, Volkow (2009) reported that patients with schizophrenia and the general population commonly abused nicotine (28.5% and 12.8%), cannabis (50.8% and 0.5%), alcohol (43.1 to 65% and 5.1%) and cocaine (23% and 0.09%) respectively. In South Africa, drug abuse is alarming and a determinant of many social, economic and medical problems. Substance dependency statistics revealed that drug abuse in South Africa is double the global average and second to none on the African continent (United Nations 2014). South Africa is rated one of the top 10 abusers of narcotics and alcohol globally, with the average age of drug dependency reported to be 12 years (United Nations 2014). 'For every 100 people, 15 have a drug problem and for every 100 Rands in circulation, 25 Rands are linked to the substance abuse problem' (Christian Addiction Support, 2016). In Nigeria, 1 in 7 persons between 15 and 64 years old had used a drug other than tobacco and alcohol in the past year, with a prevalence estimated to be at 14.4% which correspond to about 14.3 million people (United Nations Office on Drugs and Crime (UNODC) 2018). More men (with an annual prevalence of 21.8%; 10.8 million men) than women (with an annual prevalence of 7%; 3.4 million women) abused drugs in Nigeria. Abuse includes nonmedical use of illicit drugs as well as drugs that are used for the management of pains such as opioids.

The drugs commonly abused are cannabis, methamphetamine, heroin and cocaine. These drugs account for over 86% of all cases treated for abuse (United Nations 2014). It has also been reported that the abuse of codeine is on the increase (Garba, Sholey, Maryam, & Usama, 2017) and is usually a gateway to the abuse of other substances.

3.1 | The impact of drugs on male fertility

Exposure to certain drugs, particularly drugs of abuse, plays a role in male fertility. These drugs influence male fertility via various mechanisms: hormonal via the hypothalamic–pituitary–testicular axis (Figure 4) or nonhormonal (Semet et al., 2017) (Figure 5). It has become pertinent to consider recreational use of drugs when assessing the aetiology of male infertility (Fronczak et al., 2012).

3.2 | Drugs which are commonly abused

3.2.1 | Opioids

The rise in the abuse of opioid medications has become a public health challenge globally. Opioids impair male fertility via different mechanisms. At high doses, the concentrations of testosterone decline with associated hypogonadism (Abs et al., 2000). This is partly due to raised prolactin and inhibition of pituitary gonadotropin secretion. The observed hypogonadism is independent of androgen levels (Agirregoitia et al., 2006). The Leydig and germ

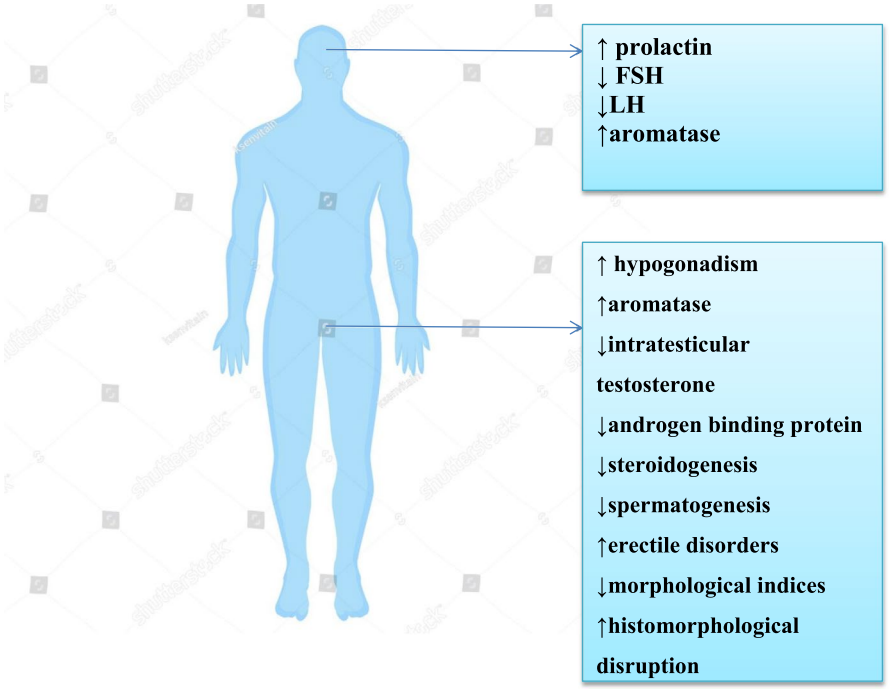

FIGURE 4 Effect of drugs and their abuse on hypothalamic–pituitary–testicular axis

cells are the sites of production of endogenous opioids. Their receptors are present throughout the testis (Albert et al., 2013). These opioids impair the secretion of androgen-binding protein which plays a role in androgen intra-testicular transport by inhibiting the Sertoli cell receptors (Aloisi et al., 2009). Morphine has also been reported to increase aromatase expression in the brain and testis and impair testicular function (Aloisi et al., 2010). Aloisi et al. (2009, 2010, 2011) documented that exogenous opioids cause DNA fragmentation and reduced semen quality. Subirán, Casis, and Irazusta (2011) reported that these effects are associated with all opioids, although less damage is observed at lower doses, by shorter-acting opioids, and by opioids with mixed receptor activity, like tramadol. Similar findings were observed in experimental mice treated with heroine. Heroin significantly reduced sperm viability, serum testosterone level and fertility rate (Fazelipour, Kiaei, & Tootian, 2010).

Long-term opioid use causes hypogonadism secondary to the suppression of gonadotropin-releasing hormone secretion by the hypothalamus (Katz & Mazer, 2009). There is a dearth of data reporting the effects of some opioids like codeine on male reproductive function. Ajayi and Akhigbe (2020) reported that chronic administration of codeine led to impaired fertility indices. Their study demonstrated that although codeine enhances sexual locomotor activity, it reduces copulatory efficiency and percentage fertility index. This is possibly via oxidative/inflammatory and caspase 3-mediated testicular damage (Akhigbe & Ajayi, 2020). Several studies have reported that opioids induce loss of libido, impotence and infertility in men (Daniell, 2002; Gratzke et al., 2010; Katz & Mazer, 2009; Schlosser, Nakib, Carre-Pigeon, & Staerman, 2007). Bar-Or, Salottolo, Orlando, and Winkler (2012) in their human study observed that tramadol prolonged ejaculation latency time. This may be beneficial in the management of premature ejaculation.

3.2.2 | Cocaine

Although Bracken et al. (1990) reported decreased sperm concentration, motility, vitality and morphology following chronic use of cocaine, in vitro study of Yelian, Sacco, Ginsburg, Doerr, and Armant (1994) on human spermatozoa demonstrated that acute exposure to high concentrations of cocaine had no significant effects on overall sperm motility and fertilising capability despite an initial decrease in straight line velocity and linearity. Hurd et al. (1992) revealed that in vitro cocaine exposure markedly decreased sperm motility and bovine mucus penetration rates. Findings of animal studies align with reports of Bracken et al. (1990) and Hurd et al. (1992). Chronic administration of high-dose cocaine has been reported to significantly reduce fertility indices, offsprings birth weights, as well as the diameter of seminiferous tubule, thickness of germinal epithelium and number of spermatids (George et al., 1996). A previous study (Rodriguez, Sanchez-Yague, & Paniagua, 1992) also observed that cocaine caused a rapid disruption of the seminiferous tubules and Sertoli cells with consequent decline in spermatogenesis. Cocaine has been reported to bind to an unidentified testicular tissue protein (Li, George, Crossland, Anderson, & Dhabuwala, 1997) to induce testicular damage via apoptosis (Li, Jiang, Rajpurkar, Dunbar, Dhabuwala, & 1999).

3.2.3 | Cannabis

The deleterious effects of *cannabis sativa* (hemp, marijuana) have been well documented. Animal studies has reported that cannabis sativa induces testicular injury evident by reduction of Johnsen score, organogonadal index and testicular total antioxidant capacity (Alagbonsi, Olayaki, & Salman, 2016), down-regulates the

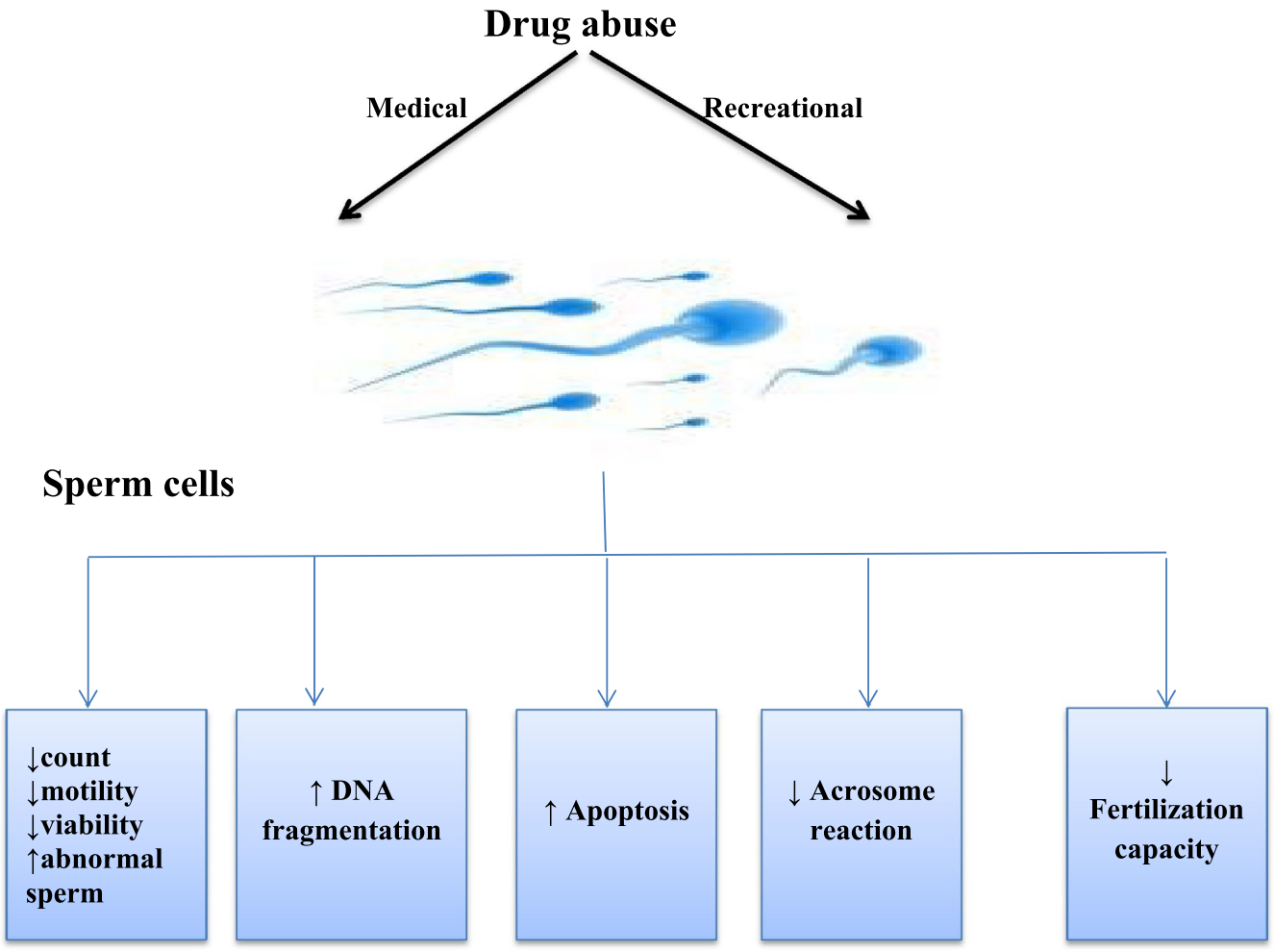

FIGURE 5 Effect of drugs and their abuse on the sperm cells

hypothalamic–pituitary–gonadal axis with resultant androgen suppression and hyperprolactinaemia (Alagbonsi & Olayaki, 2016), and triggers spermatotoxicity with consequent poor sperm quality (Alagbonsi & Olayaki, 2017). Cannabis-induced infertility was demonstrated to be via oxidative stress. In an in vitro study, tetrahydrocannabinol, the main organic composition of *Cannabis sativa* as revealed by GC-MS, also impairs sperm motility (Alagbonsi & Olayaki, 2018). Spermatotoxicity of *cannabis sativa* was demonstrated to be via cannabinoid receptor 1 (CB 1) than CB 2 (Alagbonsi & Olayaki, 2018). Interestingly, the cannabinoid-deficit Benin Republic *Cannabis sativa* was found to significantly improve sperm parameters, reduce prolactin level and enhance antioxidant status (Alagbonsi, Olayaki, Abdulrahim, Adetona, Akinyemi, 2019).

Human studies have also reported that men who abuse cannabis had poor sperm quality than men who never abused it (Gundersen et al., 2015). This deleterious effect was observed to persist even 4 weeks after withdrawal (Hembree, Nahas, & Zeidenberg, 1978). This agrees with the study of Carroll, Pottinger, Wynter, and DaCosta (2019) that observed that men who abuse cannabis have a higher risk of abnormal sperm motility and morphology. In contrary,

some studies reported a positive correlation between cannabis use and sperm parameters (Close, Roberts, & Berger, 1990; Nassan et al., 2019). The variation in these studies could be due to the dose of cannabis used/exposed to, duration of exposure and/or the specie of cannabis, whether or not it contained cannabinoid.

3.2.4 | Methamphetamine

The abuse of methamphetamine, an N-methylated amphetamine, has been reported to have adverse effects on the male reproductive function. It has been reported to decrease sperm motility and circulatory testosterone level (Yamamoto, Yamamoto, & Hayase, 1999) and induce apoptosis in seminiferous tubules in experimental mice (Yamamoto et al., 2002). Nudmamud-Thanoi and Thanoi (2011) demonstrated that methamphetamine, following acute and subacute exposure, led to significant decline in sperm count and percentage of normal sperm morphology via apoptosis. Further studies of Nudmamud-Thanoi, Sueudom, Tangsrisakda, and Thanoi (2016) documented that methamphetamine exerted an adverse effect on sperm cells by causing a significant decrease in sperm count, motility and normal morphology. This was observed to be associated with methamphetamine-induced decline in the expressions of progesterone receptor and oestrogen receptors (both ER-α and ER-β) and their respective mRNA in male germ cells and Sertoli cells. Methamphetamine has been reported to, at least partly, induce arrest of spermatogenesis by stimulating GABAergic activities in the testis (Kaewman, Nudmamud-Thanoi, & Thanoi, 2018). This was evident by significant increase in GABA concentration, and expression of GABA-AαI receptor and glutamate decarboxylase I genes following methamphetamine exposure.

This stimulant has also been implicated to significantly reduce testes index, and mRNA and protein expressions of glucose transporter 1 (GLUT1), hexokinase 1 (HK 1) and lactate dehydrogenase C (LDHC) in the testes (Yang, Shen, Chen, Li, & Xie, 2019). This could infer that the molecule also inhibits spermatogenesis by impairing glycolysis. Studies have also revealed that methamphetamine induced sperm DNA damage (Sabour et al., 2017) and altered the normal testicular histoarchitecture (Saberi et al., 2017). In an epigenetic study, Barenysa et al. (2010) demonstrated that prenatal exposure of female rats to methamphetamine led to significant delay in sexual maturation, poor sperm quality, and increased sperm DNA damage in the male offsprings.

3.2.5 | Ketamine

Ketamine, an injectable dissociative anaesthetic agent, has over time become a popular recreational drug (Britt & McCance-Katz, 2005). It is a noncompetitive antagonist at glutamatergic N-methyl-D-aspartate (NMDA) receptor. Ketamine has been reported to significantly reduce sperm motility, viability and normal chromatin dispersion (Absalan, Ghannadi, & Zabihi, 2014). This corroborates earlier findings that observed that ketamine led to testosterone suppression (Oyama, Toyota, Shinozaki, & Kudo, 1977; Carter et al., 1984). Ketamine-induced reproductive dysfunction has been shown to be, at least in part, via a calcium-dependent mechanism. In vitro studies observed that sperm exposure to ketamine significantly impaired sperm motility and ability to penetrate viscous medium, as well as progesterone-induced acrosome reaction by decreasing sperm concentration of calcium via suppression of CatSper channels (He et al., 2016).

3.3 | Drugs which are commonly used for the treatment of known diseases

3.3.1 | Immunosuppressants and chemotherapy

It has been observed that chronic use of immunosuppressants is associated with infertility in men (Drobnis & Nangia, 2017). Trials of corticosteroids have been observed to provide inconsistent findings on the quality of semen and fertility. Some studies documented improvement of semen quality, while others either reported no change or adverse effects (Omu, al-Qattan, & Abdul Hamada, 1996). Some studies have documented the use of corticosteroids in the management of antisperm antibodies and thus in the treatment of male infertility (Drobnis & Nangia, 2017). In addition, decrease in testosterone has been observed in the management of transplant rejection with corticosteroid, although this may be due to multiple immunosuppressants used in the study (Omu, al-Qattan, & Abdul Hamada, 1996). Alteration of reproductive hormones has also been observed in healthy men treated with corticosteroids (Omu et al., 1996). In a chunk of studies, low concentrations of testosterone have been observed following long-term treatment of chronic inflammatory disease with prednisone (Drobnis & Nangia, 2017; Omu et al., 1996). Dexamethasone exposure using animal models at human equivalent dose has been associated with endocrine disruption, including reduced testosterone (Orazizadeh, Hashemitabar, & Khorsandi, 2009; Orazizadeh, Khorsandi, & Hashemitabar, 2010).

It is well documented that cancer and cancer therapy impair male fertility. Chemotherapy has been demonstrated to be detrimental to spermatogenesis (Sigman, 2013). Animal studies have shown that cyclophosphamide induces oxidative stress, sperm DNA damage and also reduces sperm chromatin quality (Ghosh, Das, Ghosh, Mallick, & Debnath, 2002; Barton, Wyrobek, Hill, Robaire, & Hales, 2003; Codrington, Hales, & Robaire, 2017a; Codrington, Hales, & Robaire, 2017b). This causes a time-specific and dose-dependent adverse progeny outcomes (Downey, Hales, & Robaire, 2016; Trasler, Hales, & Robaire, 1985). Downey et al. (2016) in their study observed that cyclophosphamide altered zinc homeostasis with possible disruption of germ cell development. Human studies have also shown that men on long-term cyclophosphamide treatment have raised incidence of azoospermia and oligozoospermia (Downey et al., 2016; Qureshi, Pennington, Goldsmith, & Cox, 1972). Similarly, low sperm count

has been strongly associated with methotrexate (Padmanabhan et al., 2009; Oktar et al., 2010; Oufi & Al-Shawi, 2014). There are strong evidences that immunophilin modulators like cyclosporine, everolimus and sirolimus induce endocrine alteration and poor semen quality (Drobnis & Nangia, 2017). Sirolimus, commonly used in the prevention of organ transplant rejection, has been reported to induce dystrophy of seminiferous tubule and decreased sperm quality (Bererhi et al., 2003; Huyghe et al., 2007; Zuber et al., 2008; Chen et al., 2013; Leroy et al., 2015; VIDAL Hoptimal, 2016). These effects have however been shown to be reversible. Sirolimus impairs spermatogenesis at the spermatogonial level with consequent low germ cell lines (Rovira et al., 2012). It has been shown that sirolimus down-regulates the expression of StAR, the key protein in the rate limiting step in testosterone biosynthesis from cholesterol. This results in low intra-testicular testosterone, a factor that determines the optimal spermatogenesis. It has also been documented to impair the kiss system and thus the pulsatile release of hypothalamic GnRH (Roa et al., 2009).

With recent advances in medicare, the use of hydroxyurea (HU) in sickle cell disease (SCD) has gained more popularity. Hydroxyurea, a chemotherapeutic agent, is an FDA-approved drug for the prevention of vaso-occlusive pain in SCD. Despite its proven efficacy in the management of myeloproliferative disorders and SCD, a major drawback is its effects on the male reproductive function. Although HU-induced gonadotoxicity is reversible (Chapman, 1982), it has been reported to cause testicular atrophy, impairment of spermatogenesis and poor sperm quality in experimental animals (Evenson & Jost, 1992; Fiscor & Ginsberg, 1980; Lu & Melstrich, 1979). However, the reports of Grigg (2007) is equivocal. He reported a case series of three patients, two of whom had a decline in sperm quality following HU use while the spermogram of the third was unaltered. Contrary to this, Berthaut et al. (2017) in a prospective multicenter study in thirty-five men with severe sickle cell anaemia observed that although patients with SCD had poor sperm quality, following HU use, there was further decline in the sperm parameters. This is similar to the findings in their earlier retrospective study (Berthaut et al., 2008). A recent study by Sahoo et al. (2016) also established that although alteration in sperm quality is observed in a significant number of patients with SCD, this was aggravated by HU therapy.

3.3.2 | Tranquilisers

Studies have documented that benzodiazepines trigger erectile disorders by inhibiting the central dopaminergic pathway, a pro-erectile pathway (Droupy, 2005; VIDAL Hoptimal, 2016). This has been foreshadowed by Cook, Notelovitz, Kalra, & Kalra (1979) that demonstrated a fall in serum testosterone concentrations following a 10-day diazepam administration. Taher and Anber (2015) also observed a decline in serum gonadotropins and testosterone levels following a 8-week diazepam administration. This was associated with impaired sperm motility, reduced sperm concentration, reduced viability and increased sperm abnormalities.

3.3.3 | Anti-hypertensives

It has been hypothesised that β-blockers impair fertility by preventing the vasodilatation of corpora cavernosa. Some are also reported to reduce testosterone secretion by their actions on the central nervous system (Ferrario & Levy, 2002; Droupy, 2005; Schlosser et al., 2007; Gratzke et al., 2010; VIDAL Hoptimal, 2016). Administration of atenolol, metoprolol and propranolol for 60 days has been reported to induce significant reduction in sperm motility and increase in sperm anomalies in experimental rats (el-Sayed et al., 2017). There was also associated decline in testosterone levels and histopathological alterations in reproductive organs. These adverse effects were returned to normal after discontinuation of drugs. Similar findings were also documented by Nusier, Bataineh, and Daradka (2007) following administration of propranolol for 35 days.

Calcium channel blockers decrease sperm viability and motility and also impair spermatozoa–oocyte interaction following altered calcium transmembrane movement (Brezina, Yunus, & Zhao, 2012; Kanwar, Anand, & Sanyal, 1993; Schlosser et al., 2007). Benoff et al. (1994) revealed that calcium blockers inhibit the binding of spermatozoon to an ovum by modifying the lipid bilayer of the sperm plasma membrane. These effects have been reported to be dose- and time-dependent (Benoff et al., 1994; Kanwar et al., 1993).

Centrally acting anti-hypertensives, such as methyldopa, also induce hyper-prolactinaemia (Ferrario & Levy, 2002; De Rosa et al., 2003; Droupy, 2005; Schlosser et al., 2007; Gratzke et al., 2010; VIDAL Hoptimal, 2016). They have also been reported to induce ejaculatory dysfunction by stimulating pre-synaptic α2-adrenergic receptors and reducing central sympathetic tone (Schlosser et al., 2007; Gratzke et al., 2010; VIDAL Hoptimal, 2016).

It has been documented that digoxin alters erectile function by reducing serum testosterone levels. It has also been reported to exert anticholinergic activities thus preventing the relaxation of smooth muscle, which is essential in the distension of the corpora cavernosa during erection (Gupta et al., 1998).

Spironolactone, a potassium-sparing anti-hypertensive, has a peripheral anti-androgenic effect. It inhibits adrenal and testicular cytochromes P450 that are important in the biosynthesis of testosterone (Millsop, Heller, Eliason, & Murase, 2013). It also acts as a competitive inhibitor of androgens at the target receptor (Millsop et al., 2013). Spironolactone has been demonstrated to induce decreased libido and erectile dysfunction and decreased desire (Schlosser et al., 2007; Gratzke et al., 2010; VIDAL Hoptimal, 2016) and also impair sperm motility (Millsop et al., 2013). Thiazide diuretics are also implicated in erectile dysfunction, although this is more tolerable (Boydak et al., 2005; Droupy, 2005; Ferrario & Levy, 2002; Giuliano, Bernabe, Droupy, Alexandre, & Allard, 2004; Gratzke et al., 2010; Karavitakis et al., 2011; Manolis & Doumas, 2012; Nudell, Monoski, & Lipshultz, 2002; Schlosser et al., 2007).

Interestingly, angiotensin-converting enzyme inhibitors (ACEi) and sartans do not adversely affect erectile function. Angiotensin-converting enzyme inhibitors improves penile endothelial function and inhibits angiotensin II-induced penile detumescence (Becker

et al., 2001; Shindel, Kishore, & Lue, 2008). This class of anti-hypertensives is promising as they remain viable options in the management of erectile dysfunction. It could also be combined with other anti-hypertensives when managing hypertension with other classes of drugs that may impair fertility.

3.3.4 | Anti-diabetic drugs

The biological role of insulin and oral hypoglycaemic agents in reproductive physiology has been well elucidated. In an in vitro study, Silvestroni, Modesti, and Sartori (1992) established that the plasma membrane and acrosome are the cytological targets for the proacrosin conversion effect of insulin. Insulin has also been reported to be essential for sperm maturation (Singh, Malini, Rengarajan, & Balasubramanian, 2009). In their in vivo study, they observed that insulin replacement therapy in experimental diabetic rats elevated testosterone bioavailability, prevented diabetes-induced decline in sialic acid and carnitine concentrations, preserved glycerylphosphoryl choline and enhanced sperm quality and fertility index. Studies have revealed that insulin promotes sperm capacitation via a NO signalling pathway, thus establishing a novel association between insulin, sperm physiology and NO (Aquila, Giordano, Guido, Rago, & Carpino, 2013; Carpino, Rago, Guido, Casaburi, & Aquila, 2010).

Similarly, oral hypoglycaemic agents have been observed to be beneficial to male reproductive functions. Studies have reported that metformin, a biguanide, when administered alone or in combination with other drugs that exerts positive influence on male reproduction, protects against testicular and spermatic injury in diabetic rats (Ebokaiwe et al., 2020; Nasrolahi, Khaneshi, Rahmani, & Razi, 2013; Nna, Bakar, Ahmad, Eleazu, & Mohamed, 2019). This has been linked with its potential to attenuate diabetes-induced hormonal suppression, oxidative stress, inflammation and apoptosis. Interestingly, metformin has also been shown to improve testicular function and sperm quality in obesity. Metformin decreased ectopic lipid testicular accumulation, ameliorated oxidative testicular damage, abrogated high-fat-diet-induced blood-testicular-barrier injury and enhanced fertility in obese male mice (Ye et al., 2019). McPherson and Lane (2020) also observed that metformin treatment restored sperm function and foetal growth without requiring weight loss in high-fat diet obese male mice. Furthermore, Grandhaye et al., (2020) provided evidence to suggest that metformin improved the quality of canine cryopreserved semen via AMPK pathway.

Glimepiride, a sulphonylurea, has been reported to demonstrate an inhibitory effect on nicotinamide–streptozotocin-induced nuclear damage and sperm abnormality (Rabbani, Devi, & Khanam, 2009). This was observed to be associated with its potential to improve antioxidant status. Glimepiride has also been shown to enhance circulatory concentration of testosterone in a pilot study involving middle-aged type II diabetic men (Wong et al., 2015).

Pioglitazone, a thiazolidinedione, also exerts an anti-oxidant effect. When given in combination with metformin or glimepiride, it attenuates diabetes-induced nuclear damage and poor sperm quality by improving the redox status. (Rabbani et al., 2009).

3.3.5 | Anti-inflammatory drugs

Although there are just a few human studies reporting the effects of nonsteroid anti-inflammatory drugs (NSAIDS) on male fertility, the available studies reported a less effect when compared to the effects of opioids (Subirán et al., 2011). Paracetamol has been shown to induce sperm abnormalities and sperm DNA damage (Subirán et al., 2011; Vuong, Van Uum, O'Dell, Lutfy, & Friedman, 2010). In rodents, it has been shown to cause seminiferous tubules destruction (Subirán et al., 2011). The effects of NSAIDS including acetylsalicylate are dose-dependent and reversible (Martini, Molina, Tissera, Ruiz, & de Cuneo, 2003; Mendonca, Khamashta, Nelson-Piercy, Hunt, & Hughes, 2000). These drugs inhibit the cyclo-oxygenase enzymes with resultant impairment of the synthesis of prostaglandin, which is possibly essential in testicular steroidogenesis, spermatogenesis regulation and acrosome reaction of the spermatozoa (Joyce, Nuzzo, Wilson, & Zaneveld, 1987).

Sulfasalazine, an immunosuppressant commonly used in the management of inflammatory conditions like rheumatoid arthritis, ulcerative colitis and Crohn's disease, has been shown to reversibly alter sperm parameters following long-term use. Chronic use of sulfasalazine leads to decreased sperm concentration, motility and morphology (Leroy et al., 2015). It has also been associated with oligoasthenospermia (Semet et al., 2017). It has been reported to impair the hypothalamic–pituitary–testicular axis with consequent decline in the biosynthesis of testosterone (Semet et al., 2017). Alonso et al. (2009) also reported that sulphapyridine, its active metabolite, induces oxidative stress with a decline in sperm quality. Although the mechanism remains unclear, sulfasalazine-induced reproductive toxicity is reversible (Niederberger, 2002; Nudell et al., 2002; Østensen et al., 2006; Grunewald, Paasch, & Glander, 2007; Schlosser et al., 2007; Palomba et al., 2014; VIDAL Hoptimal, 2016).

3.3.6 | Phosphodiesterase inhibitors

Another common drug of abuse is the phosphodiesterase inhibitors (PDE inhibitors). The nonspecific PDE inhibitors, especially the methylxanthines: caffeine, pentoxifylline (PTX) and theophylline, have been reported to induce sperm motility in vitro and are used to treat sperm prior to artificial insemination (Park, Choi, Choi, Yim, & Roh, 2015). In vivo studies have shown less dramatic effects. Very high doses of caffeine impair reproductive function in experimental animals (Sadeu, Hughes, Agarwal, Foster, 2010; Saadat, Ahmadi, & Panahi, 2015). The specific PDE5 inhibitors, such as sildenafil and tadalafil, are useful in the treatment of erectile dysfunction, premature ejaculation, pulmonary hypertension and lower urinary tract symptoms seen in benign prostatic hyperplasia (BPH). The expression of PDE5 in the contractile tissues of the male reproductive tract helps to increase contractility (Alp et al., 2012; Uckert, Bazrafshan, Sonnenberg, & Kuczyk, 2009). Some PDE5 inhibitors cause raised concentrations of testosterone (Andric, Janjic, Stojkov, & Kostic, 2010; Spitzer et al., 2013). These drugs have minimal effects on semen quality when used

short-term prior to sexual intercourse (Aversa et al., 2000). In human studies, Pomara et al. (2007) observed no adverse effects on semen quality following long-term exposure to PDE5 inhibitors. Randomised control trials in infertile men have reported a rise in semen quality (Purvis, Muirhead, & Harness, 2002; Rago et al., 2012). This agrees with reports in animal studies at human equivalent doses (HED), however a study in ageing rats observed progressive decline in epididymal sperm quality with associated seminal tubules degeneration (Özgür et al., 2014). Sildenafil elevates serum testosterone levels along with dihydrotestosterone and oestradiol (Spitzer et al., 2013). This is via a direct action on the testis and possibly on adrenal steroidogenesis.

3.3.7 | Alpha-adrenergic blockers

Although they are antagonists of α_1-adrenergic receptors of the smooth muscle and anti-hypertensives, they remain the first-line drugs in the management of lower urinary tract symptoms (LUTS) seen in BPH. In spite of their efficacy in alleviating LUTS, some α_1-adrenergic blockers have been reported to cause and/or aggravate ejaculatory dysfunction (EjD) (Carbone & Hodges, 2003; Hisasue et al., 2006; Kimsakulvech, Suttiyotin, & Pinyopummin, 2015), usually retrograde ejaculation and anejaculation. A study revealed that tamsulosin-induced ejaculatory dysfunction following a 5-day treatment in healthy men was characterised by reduced ejaculation volume or anejaculation, and not retrograde ejaculation (Hellstrom & Sikka, 2006). Tamsulosin has been reported to cause a higher rate of EjD than alfuzosin (Hellstrom & Sikka, 2009). Though the mechanism involved in tamsulosin-induced EjD is yet unclear, it is likely via its interaction with centrally located serotonin (5HT) and dopamine (D2-like) receptors (Andersson & Wyllie, 2003; Giuliano, Clement, Denys, Alexandre, & Bernabe, 2006), bladder neck closure impairment, contractions of seminal vesicle and bulbospongiosus muscle (Giuliano et al., 2004, 2006), and alterations in contractions of the vas deferens (Tambaro et al., 2004). However, it is worthy to note that alpha blockers have not been implicated in erectile dysfunction (Droupy, 2005; Giuliano et al., 2006).

It is astonishing that tamsulosin does not only cause EjD, it also alters sperm quality. In a study by Hellstrom and Sikka (2006), forty-eight healthy men were exposed to a 5-day treatment of tamsulosin and alfuzosin (0.8 mg, OD and 10mg QD respectively). It was observed that tamsulosin had an adverse effect on semen viscosity, sperm concentration, sperm motility and total sperm count. On the other hand, sperm parameters of subjects who received alfuzosin were similar to those of the placebo. The study of Kimsakulvech et al. (2015) similarly demonstrated a reversible dose-dependent alteration in sperm quality following tamsulosin use. The variation in the effects of tamsulosin and alfuzosin on sperm quality is likely due to their structural difference; tamsulosin is a sulphonamide derivative while alfuzosin is a quinazoline derivative (Hellstrom & Sikka, 2009).

3.3.8 | Anti-androgen

Finasteride is a common anti-androgen. It is a specific 5α-reductase inhibitor that is used in the management of BPH. Finasteride inhibits the conversion of testosterone to dihydrotestosterone, an androgen with a stronger affinity for androgen receptor. Samplaski, Lo, & Grober, (2013) Jarvi observed that even at low doses, finasteride may lead to decline in sperm counts in some men. This effect is reversible following cessation. However, it led to an irreversible alteration in male hormone profile, sperm motility and sperm morphology. However, this is not in tandem with the findings of Rittmaster et al. (1992) that observed no discernible effect on serum gonadotropin levels following a 28-day treatment with finasteride. Surprisingly, Amory et al. (2007) observed that the decrease in dihydrotestosterone caused by finasteride and dutasteride (administered singly) is associated with reversible decline in sperm parameters.

In a standardised interview with 71 apparently healthy men within ages 21 and 46, Irwig and Kolukula (2011) observed that finasteride use is significantly associated with low libido and arousal, erectile dysfunction and poor orgasm. The study of Traish, Hassani, Guay, Zitzmann, and Hansen (2011) also revealed impaired libido and erectile dysfunction following finasteride and dutasteride use. Overstreet et al. (1999) observed that finasteride had no effect on sperm quality. However, they observed a significant decline in ejaculate volume, prostate volume and serum prostate specific antigen. These effects were reversible after drug discontinuation. Vincent and Zini (2011) in their documented case report demonstrated a strong association between finasteride use and sperm DNA damage in couples with secondary infertility. In their report, the sperm DNA fragmentation index (DFI) at presentation was 30% and remained unchanged after two months. Three months after cessation of finasteride, DFI reduced to 21%, and to 16.5% by six months after cessation.

Cyproterone is also a commonly used anti-androgen in androgen-dependent conditions like prostate cancer, transgender, excessive hair growth and acne. It inhibits testicular testosterone synthesis and also competitively inhibits the binding of 5α-dihydrotestosterone to its cytosolic receptor at the target cells (Schlosser et al., 2007; VIDAL Hoptimal, 2016). This medication has been implicated to cause erectile dysfunction and impair libido. It has also been reported to reversibly damage sperm cells. In a prospective study by Schroder, Collette, de Reijke, and Whelan (2000), cyproterone was observed to impair erections and sexual activity. This effect was not seen in subjects on nonsteroidal anti-androgens. In a prospective study carried out 20 years before this, Wang and Yeung (1980) demonstrated that cyproterone led to reduced sperm concentration, motility and impaired morphology after 16 weeks of use.

3.3.9 | Anabolic steroids

Androgen abuse has increased possibly due to its anabolic effect. The prescription of exogenous androgens is only appropriate after investigation and confirmation of hypogonadism in individuals who do not intend to father a child (Amory, Page, & Bremner, 2006; Piotrowska,

Wang, Swerdloff, & Liu, 2017). However, when fertility is desired, there are alternative drugs that can be used alone or in combination in hypogonadism (Ohlander, Lindgren, & Lipshultz, 2016). Although anabolic steroids have the potential to increase strength and muscle mass, they are all androgenic (El Osta, Almont, Diligent, Hubert, Eschwège, & Hubert, 2016). Contrary to the popular misconception, testosterone use impairs fertility (Samplaski et al., 2014). It inhibits spermatogenesis by impairing the normal physiological feedback mechanism in response to low circulating levels of testosterone (McBride & Coward, 2016; Samplaski et al., 2014) via inhibition of the hypothalamic–pituitary–gonadal axis. This causes decline in the secretion of gonadotropins needed to stimulate endogenous biosynthesis of testosterone and consequent impairment of spermatogenesis (Liu, Swerdloff, Christenson, Handelsman, & Wang, 2006). It is noteworthy that the normal concentrations of testicular testosterone are about 100 times that in the circulation. These high concentrations are necessary for optimal spermatogenesis. Hence, even with normal concentrations of circulating testosterone, spermatogenesis could be impaired if there are insufficient gonadotropin and testicular testosterone levels (McBride & Coward, 2016; Nieschlag & Vorona, 2015).

Exogenous testosterone triggers a negative feedback on the hypothalamic–pituitary–gonadal axis, thus inhibiting gonadotropin synthesis. Abusers of this steroid have been reported to present with oligozoospermia or azoospermia and associated abnormality in sperm motility and morphology (Dohle, Smit, & Weber, 2003). Animal studies documented Leydig cell alterations and cellular morphology anomalities following exposure to anabolic androgenic steroid (Feinberg, Lumia, & McGinnis, 1997; Grokett, Ahmad, & Warren, 1992). Although there was a reversal of these effects after discontinuation, reversal was not total (Nagata et al., 1999). This is similar to findings in human studies that reported altered sperm parameters which returned to normal after 4 to 12 months of cessation (Gazvani et al., 1997; Knuth, Maniera, & Nieschlag, 1989; Koskinen, Marttila, & Katila, 1997; Turek, Williams, Gilbaugh, & Lipshultz, 1995). Shokri et al. (2010) documented the association between apoptosis and high doses of nandrolone. Shokri and his colleagues observed an increase in the rate of apoptosis of spermatogenic cells following administration of this anabolic androgenic steroid.

In a cross-sectional case–control study, Rasmussen et al. (2016) recruited 37 current abusers, 33 former abusers and 30 nonabusers of anabolic androgenic steroid within age 18 and 50 years. Their study revealed that former abusers had significantly reduced concentrations of plasma testosterone and higher frequencies of symptoms indicative of hypogonadism than in their healthy control counterparts years after drug discontinuation. Current abusers had significantly reduced anti-mullerian hormone and inhibin B indicating suggestive of impaired spermatogenesis. These findings are not in consonance with findings of the online survey by Avant et al. (2018) that reported unexpectedly high fertility rate among anabolic steroid users despite continued use. Although the variation observed by Avant and his colleagues could be due to the subjectivity of their study.

3.3.10 | Antidepressants

Serotonin reuptake inhibitors (SRI) and tricyclic antidepressants are common first-line drugs in the management of depression. Paroxetine, a known selective serotonin reuptake inhibitors (SSRI), has gained popularity in its use to experimentally induce sexual dysfunction (Ademosun, Adebayo, & Oboh, 2019a, 2019b; Ajiboye, Nurudeen, & Yakubu, 2014; Yakubu & Atoyebi, 2018). They have been implicated in infertility via a prolactin-dependent pathway. SRIs have also been reported to adversely alter sperm parameters, particularly sperm count and motility (Nudell et al., 2002; De Rosa et al., 2003; Schlosser et al., 2007; Tanrikut & Schlegel, 2007). SRIs especially paroxetine induce sperm DNA fragmentation (Tanrikut & Schlegel, 2007; Safarinejad, 2008; Tanrikut, Feldman, Altemus, Paduch, & Schlegel, 2010; Brezina et al., 2012). Human studies have also documented sexual dysfunction in men who are on SSRIs (Jacobsen, Mahableshwarkar, Chen, Chrones, & Clayton, 2015; Waldinger, van Coevorden, Schweitzer, & Georgiadis, 2015). Serotonin receptors, 5-HT_{2C} and 5-$HT_{1A,}$ play vital roles in sexual function. Stimulation of 5-HT_{2C} receptors enhances erections and impairs ejaculation, while stimulation of 5-HT_{1A} receptors facilitates ejaculation and, sometimes, impairment of erection. Hence, SRIs prolong the onset of copulation and ejaculation when copulation begins (Hull, Muschamp, & Sato, 2004). Furthermore, SRI-induced impaired sexual function is linked with a reduction in dopamine release in the mesolimbic tract (Hull et al., 2004). Dopamine enhances sexual motivation, copulatory proficiency and genital reflexes. In the mesolimbic tract and medial preoptic area, dopamine stimulates sexual behaviour and genital reflexes respectively. In the medial preoptic area, dopamine release is via testosterone NOs/NO-dependent mechanisms. This explains the role of SRI-induced hyper-prolactinaemia in testosterone suppression and testosterone-dependent sexual functions. SRIs have also been reported to directly inhibit NO production and increase noradrenaline concentrations (Clayton, El Haddad, Iluonakhamhe, Martinez, & Schuck, 2014; Giuliano & Droupy, 2013; Taylor et al., 2013).

Monoamine oxidase inhibitors (MAOIs), another class of antidepressant, which are rarely used, are less associated with hyper-prolactinaemia (De Rosa et al., 2003; Althof et al., 2010; Gratzke et al., 2010; Giuliano & Droupy, 2013; Taylor et al., 2013; Clayton et al., 2014; VIDAL Hoptimal, 2016).

3.3.11 | Antipsychotics

Similar to antidepressants, antipsychotics impair sexual functions. Typical antipsychotics induce hyper-prolactinaemia via a dopamine-dependent mechanism, whereas atypical antipsychotics do not alter prolactin concentrations significantly (Giuliano & Droupy, 2013; Gratzke et al., 2010; De Rosa et al., 2003). Typical antipsychotics have been reported to alter spermatogenesis and sperm quality (De Rosa et al., 2003; Schlosser et al., 2007). They are also associated with impaired libido, erection, orgasm and ejaculation (Giuliano & Droupy, 2013; Gratzke et al., 2010).

3.3.12 | Antiepileptics

Antiepileptics have been implicated as risk factors in infertility. They induce male infertility via several mechanisms. Carbamazepine, valproate and phenytoin reduce sperm motility via interference with sperm membrane function (Semet et al., 2017). Carbamazepine directly induces necrosis of germ cells, while valproate causes reduced testicular size with consequent impairment of spermatogenesis (Brezina et al., 2012; Isojarvi et al., 2004; Isojarvi, Taubøll, & Herzog, 2005; de Oliva & Miraglia, 2009). Valproate has also been reported to induce reduction in L-carnitine/T-carnitine ratio (Isojarvi et al., 2004, 2005). Although reports on the effects of newer generations of antiepileptics such as levetiracetam are scanty, the few in existence also implicate them in infertility pathogenesis. Ceylan, Yalcin, Bayraktutan, Karabulut, & Sonkaya et al. (2016) observed decreased sperm concentration, impaired sperm morphology and sperm functionality in 26 males on levetiracetam monotherapy. The altered sperm indices were not associated with alterations sex hormone levels. Their findings corroborate earlier observations of Xiaotan et al. (2013) among Chinese Han men.

3.3.13 | Cimetidine

Cimetidine, an antihistamine that acts via blocking H_2-receptor and is commonly used in the management of peptic ulcer disease and gastro-oesophageal reflux disease, has been documented to possess anti-androgenic activities. Experimental studies revealed that cimetidine causes testicular damage, leading to abnormal spermatogenesis. A similar finding was reported in human studies (Franca et al., 2000; Millsop et al., 2013; Nudell et al., 2002; Schlosser et al., 2007). It was observed to cause a reversible decline in sperm count.

3.3.14 | Anticholesterolemics

Statins inhibit HMG-CoA reductase, a vital enzyme in cholesterol biosynthesis. Since cholesterol is precursors of steroid hormone, inhibition of cholesterol synthesis by statins possibly reduces the circulating levels of testosterone with consequent reduced libido and erectile dysfunction (Bruckert, Giral, Heshmati, & Turpin, 1996; Do, Huyghe, Lapeyre-Mestre, Montastruc, & Bagheri, 2009; Gratzke et al., 2010; Rizvi, Hampson, & Harvey, 2002; Saltzman, Guay, & Jacobson, 2004; Solomon et al., 2006).

3.3.15 | Anti-infectives

Antimicrobial/anti-infective drugs are also widely abused particularly in developing countries. Although in vivo data are lacking, most antibiotics alter sperm motility in vitro (Semet et al., 2017). Nitrofurantoin has been reported to impair spermatogenesis via a direct gonadotoxic effect at the level of primary spermatocytes and spermatids (VIDAL Hoptimal, 2016). At high dose, nitrofurantoin halts the maturation of germ cell by preventing carbohydrate and oxygen uptake that are important for optimal function of cells involved in spermatogenesis (VIDAL Hoptimal, 2016). Antibiotic-induced oligospermia has been reported to be reversible after antibiotic withdrawal (Khaki et al., 2008; Hamada et al., 2011). However, in cases of infections of the testes and epididymis, antibiotic therapy is beneficial due to its positive effect on sperm parameters (Nudell et al., 2002; Schlosser et al., 2007; Khaki et al., 2008; Yaniz, Marco-Aguado, Mateos, & Santolaria, 2010; Hamada et al., 2011; Boitrelle et al., 2012; Millsop et al., 2013; VIDAL Hoptimal, 2016). Experimental study of Fahmy et al. (2017) revealed that a 2-week treatment with amoxicillin-clavulanic acid at human equivalent dose led to abnormal sperm morphology. Histological examination of cut sections of the testes also revealed decline in the number of spermatozoa, pyknotic cells and congestion of blood vessels. This is associated with atrophy of some seminiferous tubules with disorganised and degenerative changes in the spermatogenic cells of the seminiferous tubules.

Metronidazole has also been reported to induce infertility. Study of Grover et al. (2001) showed that intraperitoneal administration of metronidazole for 30 days led to sperm DNA damage and decline in circulating gonadotropins and testosterone. Elazab, el-Komy, El-Nahas & El-Ashmawy (2004) also found out that a 14-day treatment of mice with metronidazole led to significant decline in the weights of reproductive and accessory sexual organs. They also observed a rise in the number of abnormal spermatozoa and a reduction in motile spermatozoa following metronidazole treatment. These findings were associated with reduced testosterone level. This is in consonance with the later findings of Mudrya, Palermo, Merani, and Carballo (2007) that demonstrated metronidazole-induced alterations in murine spermatozoa morphology. Observations of Sohrabia, Alipour, and Mellatic (2007) in male rats corroborates these findings. Sohrabia et al. (2007) confirmed that metronidazole suppressed spermatogenesis and sex hormones. Karbalay-Doust and Noorafshan (2011) also reported that metronidazole caused an increased in sperm abnormality and a significant reduction in sperm concentration, sperm motility and serum testosterone. Although metronidazole did not affect reproductive organ weights and their histoarchitecture, and sperm indices at a lower dose (250 mg/kg BW), these parameters were adversely altered at a higher dose (500 mg/kg BW) Kumari and Singh (2013). It was also shown that although this molecule does not affect libido, it significantly reduced fertility index (Kumari & Singh, 2018).

Ornidazole, an antimicrobial commonly used to treat genital tract infections, has also been associated with male infertility at high doses. It exerts a reversibly antifertility effect (Bone, Jones, Kamp, Yeung, & Cooper, 2000; Cooper, Yeung, Skupin, & Haufe, 1997; McClain & Downing, 1988a, 1988b; Oberländer, Yeung, & Cooper, 1994). It significantly reduced sperm motility and epididymal secretions at high doses in experimental rats (Oberländer et al., 1994). Metabolites of ornidazole are inhibitors of glycolytic enzymes, including glyceraldehyde-3-phosphate dehydrogenase and triosephosphate isomerase,

TABLE 1 The evidence for drug-induced reproductive dysfunction

Medication category	Medication	Human studies	Animal studies	Impact on male fertility	References
Immunosupressant	Dexamethasone, corticosteroids	+	+	Endocrine disruption	Orazizadeh et al., 2009; Orazizadeh et al., 2010
Chemotherapy	Cyclophosphamide, cyclosporine, sirolimus*, everolimus, hydroxyurea*	+	+	Sperm DNA damage, down-regulates the expression of StAR	Ghosh et al., 2002; Barton et al., 2003; Codrington, Hales, & Robaire, 2017a; Codrington, Hales, & Robaire, 2017b; Chapman, 1982; Berthaut et al., 2017
Opioids	Morphine*, tramadol*, codeine	+	+	Up-regulates aromatase expression, sperm DNA fragmentation, loss of libido, impaired steroidogenesis	Aloisi et al. (2009, 2010, 2011); Akhigbe & Ajayi, 2020
Tranquilisers	Diazepam*	−	+	Altered sperm quality, erectile dysfunction	Droupy, 2005; HVIDAL Hoptimal, 2016
Anti-hypertensives	B-blockers*	−	+	Altered spermatozoa, erectile dysfunction	Ferrario & Levy, 2002 Schlosser et al., 2007; Brezina et al., 2012
	Calcium channel blocker	−	+	Impaired fertilization capacity of the sperm	Gratzke et al., 2010; HVIDAL Hoptimal, 2016 Gupta et al., 1998
	Centrally acting drugs	+	+	Erectile dysfunction	Karavitakis et al., 2011; Manolis & Doumas, 2012
	Digoxin	+	−	Erectile dysfunction	
	Spironolactone	+	+	Erectile dysfunction, impaired libido	
Anti-inflammatory drugs*	NSAIDS	+	+	Sperm DNA damage, altered sperm parameters, impaired Steroidogenesis	Vuong et al., 2010; Subirán et al., 2011
	Sulfasalazine	+	+	Altered sperm parameters, impaired HPG axis	Østensen et al., 2006; Leroy et al., 2015
Phosphodiesterase inhibitors	Caffeine, sildenafil and tadalafil,	−	+	Altered sperm quality	Sadeu, Hughes, Agarwal, & Foster, 2010; Özgür et al., 2014; Saadat et al., 2015
Alpha-adrenergic blockers	Tamsulosin*	+	+	Ejaculatory dysfunction, altered sperm quality	Carbone & Hodges, 2003; Hisasue et al., 2006; Kimsakulvech et al., 2015
Anti-androgens*	Finasteride, cyproterone	+	+	Altered sperm parameter, reduced libido, erectile dysfunction, sperm DNA damage	Amory et al., 2007; Vincent & Zini, 2011
Anabolic steroid*	Testosterone	+	+	Impaired HPG axis, altered sperm quality	Samplaski et al., 2014; McBride & Coward, 2016
Antidepressants	Serotonin reuptake inhibitors	+	+	Sexual dysfunction, altered sperm parameter, sperm DNA fragmentation	Yakubu & Atoyebi, 2018; Ademosun et al., 2019a
	Monoamine oxidase inhibitors	+	+	Impaired HPG axis	De Rosa et al., 2003; Althof et al., 2010; Gratzke et al., 2010; Giuliano & Droupy, 2013; Taylor et al., 2013

(Continues)

TABLE 1 (Continued)

Medication category	Medication	Human studies	Animal studies	Impact on male fertility	References
Antiepileptics	Carbamazepine, valproate, phenytoin and levetiracetam	+	+	Impaired sperm motility, impaired steroidogenesis, germ cell damage	Isojarvi et al., 2004; Isojarvi et al., 2005; de Oliva & Miraglia, 2009; Brezina et al., 2012
Antihistamine	Cimetidine	+	+	Testicular damage, impaired Steroidogenesis	Franca et al., 2000; Nudell et al., 2002; Schlosser et al., 2007; Millsop et al., 2013
Anticholesterolemics	Statins	+	+	Reduced testosterone, reduced libido, erectile dysfunction	Saltzman et al., 2004; Solomon et al., 2006; Do et al., 2009
Antibacterial*	Nitrofurantoin	+	+	Gonadotoxic	Khaki et al., 2008; Hamada et al., 2011
	Amoxicillin-clavulanic	+	+	Altered sperm quality	Fahmy et al. (2017)
	Metronidazole	−	+	Sperm DNA damage, impaired HPG axis	Elazab, el-Komy, El-Nahas & El-Ashmawy (2004)
	Ornidazole	−	+	Impaired sperm motility	Oberländer et al., 1994; Cooper et al., 1997; Bone et al., 2000
	Tetracycline	−	+	Altered sperm parameters	Raji et al., 2007; Farombi, Ugwuezunmba, Ezenwadu, Oyeyemi, & Ekor, 2008
	Anti-tuberculosis\ (rifampicin, isoniazid, pyrazinamide, ethambutol)	−	+	Increased oxidative damage, increased DNA fragmentation, and decreased fertilization capacity	Shayakhmetova et al., 2012
Anti-parasitic*	Niridazole, Chloroquine	+	+	Impaired spermatogenesis and sperm acrosome reaction	Antohi et al., 2011; Østensen et al., 2006
Antifungal*	Ketoconazole	+	+	Impaired steroidogenesis	Millsop et al., 2013; VIDAL Hoptimal, 2016
Antiviral*	Ribavirin	+	+	Induces sperm DNA apoptosis	Narayana, D'Souza, & Seetharama, 2002; Durazzo et al., 2006; Pecou et al., 2009; Hofer et al., 2010
	HAART	+	+	Gonadotoxicity, impaired Steroidogenesis, altered sperm parameters	Adana et al., 2018; Awodele et al., 2018; Savasi et al., 2018

Note: + denotes yes; − denotes no, * denotes reversibility following drug withdrawal.

Abbreviations: HAART, highly active antiretroviral therapy; HPG, hypothalamic–pituitary–gonadal axis.

in spermatozoa (Jones & Stevenson, 1983; Jones, Stevenson, Hutton, & Dawson, 1981; Oberländer, Yeung, & Cooper, 1996; Stevenson & Jones, 1985). Studies have revealed a reduction in sperm kinetics in ornidazole-treated rats when spermatozoa were released into medium containing only glucose as substrate but not when pyruvate and lactate were added (Cooper et al., 1997; Yeung, Oberländer, & Cooper, 1995). This confirms that ornidazole impairs glucose utilisation by spermatozoa, which is not just important for sperm motility but also for binding to and penetration of the zona pellucida.

Tetracycline, a broad-spectrum antibiotic, has also been observed to induce male infertility in experimental animals. Tetracycline administered for 14 days was shown to reduce sperm concentration, motility and viability, with associated increase in abnormal sperm (Farombi, Ugwuezunmba, Ezenwadu, Oyeyemi, & Ekor, 2008). It was also found to adversely affect reproductive organ weights and histoarchitecture. These affects were via oxidative stress. The findings of Farombi and his colleagues corroborate the findings of Raji et al. (2007) that reported that tetracycline when administered for 8 weeks led to reduced weights of reproductive organs, sperm count and motility, as well as serum testosterone.

Although there is a paucity of data reporting the effects of anti-tuberculosis drugs on fertility profile, the few in existence

associated anti-Koch's with impaired reproductive function. Studies of Shayakhmetova, Bondarenko, and Kovalenko, (2012) revealed that co-administration of ethambutol, isoniazid, rifampicin and pyrazinamide at human equivalent therapeutic doses during the period of spermatogenesis led to significant oxidative testicular and sperm damage, as well as a decline in anti-oxidant buffering capacity in the testis. There was also a significant rise in DNA fragmentation and decline in fertilisation capacity following anti-Koch's treatment.

Similarly, anti-parasitic drugs have been reported to be toxic to eukaryotic cells with significant potential for reproductive dysfunction (Antohi, Gales, & Nechifor, 2011). In humans, only niridazole has been reported to induce reversible spermatogenic arrest in men with schistosomiasis (Antohi et al., 2011). Chloroquine is an anti-protozoan drug that is commonly used in the treatment of malaria. It is a lysosome stabiliser that acts as a protease inhibitor (Østensen et al., 2006). Although studies on the effects of chloroquine on male fertility are insufficient (Grunewald et al., 2007; Millsop et al., 2013; Østensen et al., 2006), it has been reported to impair spermatozoa acrosome reaction and reduce sperm fertilisation capacity (Grunewald et al., 2007).

Ketoconazole, an antifungal that impairs the action of cytochromes P450 enzymes, is essential in steroidogenesis. The blockade of the 17α-hydroxylase and desmolase impairs the biosynthesis of androgens and intra-testicular testosterone (Millsop et al., 2013) with a reversible alteration in sperm quality (Millsop et al., 2013; VIDAL Hoptimal, 2016).

Antiviral drugs have also been linked with male reproductive dysfunction. Ribavirin reversibly alters germ cells (Durazzo et al., 2006; Pecou et al., 2009). Inosine monophosphate dehydrogenase, a key enzyme in the biosynthesis of DNA and RNA guanosine triphosphate, is inhibited by ribavirin, hence impairing cell growth. This induces apoptosis and defective multiplication of germ cells of the seminal epithelium (Narayana, D'Souza, & Seetharama, 2002; Durazzo et al., 2006; Pecou et al., 2009; Hofer et al., 2010; VIDAL Hoptimal, 2016).

A number of studies revealed that antiretroviral drugs alter sperm parameters, particularly motility. Studies of Azu et al. (2014) observed that rats treated with human therapeutic dose equivalents of HAART cocktail (lamivudine, stavudine and nevirapine) developed extensive seminiferous tubular atrophy, necrosis and hypocellularity in the histoarchitectural patterns. HAART led to destructive histomorphopathological alterations in the testes causing tubular atrophy and altered morphometric indices. Awodele et al. (2018) studied the effect of different HAART combinations (tenofovir/lamivudine, atazanavir/ritonavir, zidovudine/lamivudine/nevirapine and tenofovir/lamivudine/efavirenz) on reproductive profile. It was observed that HAART led to reductions in the weight of testes and epididymis, sperm count and motility, LH, FSH and testosterone in male rats. Human studies have also reported a reduction in sperm volume and motility, and an increase in sperm DNA fragmentation following HAART use (Bujan et al., 2007, Savasi et al., 2018). These findings are similar with those of animal studies (Adana et al., 2018). Although the deadly infectious disease itself impairs fertility (Bujan et al., 2007; Savasi et al., 2018; Adana et al., 2018), the use of HAART further deteriorate fertility profile.

4 | CONCLUSIONS

Inappropriate drug use, particularly drug abuse, adversely affect male fertility. These drugs impair male fertility in different ways via various mechanisms. Documented studies have revealed that common effects include impairment of hypothalamic–pituitary–gonadal functions, increased sperm DNA fragmentation and apoptosis, and reduced sperm quality. This review provides a useful database for evaluating drug-induced male infertility (Table 1). Further studies on experimental animals should be conducted to assess the effects of some other medications on fertility. Human studies should also be carried out to confirm whether or not these effects are observed in humans.

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