INTRODUCTION
Infertility is defined as the inability to achieve a clinical pregnancy after 12 months of unprotected sexual intercourse. Males are solely responsible for 20%–30% of the infertility cases while contributing to about 50% of cases overall (Agarwal, Mulgund, Hamada, & Chyatte, 2015). Approximately 7% of men worldwide are infertile (Nieschlag, Behre, & Nieschlag, 2010).

Male infertility is strongly correlated with excess reactive oxygen species (ROS) in human semen (Agarwal, Sharma, et al., 2006; Aitken, Clarkson, Hargreave, Irvine, & Wu, 1989). ROS are oxygen-derived free radicals, which, at low levels, are required for sperm capacitation, hyperactivation, acrosome reaction and spermatozoa–oocyte fusion. However, excess ROS overwhelm the neutralising capability of antioxidants in the seminal plasma, causing oxidative stress (OS) and, consequently, DNA damage in the nucleus and mitochondria (Sawyer, Mercer, Wiklendt, & Aitken, 2003) (See Figure 1).

It is imperative to delineate the mechanisms of this damage in spermatozoa to better develop therapeutic agents and/or take preventative measures to combat male infertility. This review focuses on the main sources of OS, how OS causes sperm DNA damage and the types of damage that can occur. The clinical consequences of ROS-mediated damage on the reproductive system are also discussed.

1.1 | Sources of ROS
OS, defined as a physiological redox imbalance, occurs due to either an overabundance of ROS or a deficiency in antioxidants. Infertile men can have in their seminal plasma, elevated levels of ROS and decreased antioxidant concentrations (Iwasaki & Gagnon, 1992; Mahfouz, Sharma, Sharma, Sabanegh, & Agarwal, 2009). Contributing factors to OS, either from an endogenous or exogenous source, include genitourinary infections, varicocele, metabolic syndromes, cigarette smoking, alcohol abuse, recreational drug abuse, ionising radiation, mobile phone use, psychological stress, strenuous exercise, spinal cord injury and environmental pollution (Adams, Galloway, Mondal, Esteves, & Mathews, 2014; Agarwal, Prabakaran, & Allamaneni, 2006; Bisht & Dada, 2017; Condorelli, Russo, Cologero, Morgia, & La Vignera, 2017; De Lamirande, Leduc, Iwasaki, Hassouna, & Gagnon, 1995; Harlev, Agarwal, Gunes, Shetty, & du Plessis, 2015; Mostafa et al., 2017; Sharma, Harlev, Agarwal, & Esteves, 2016).

The main sources of ROS are immature spermatozoa and leukocytes in the seminal plasma (reviewed in Henkel, 2011). Immature spermatozoa contain a surplus of residual cytoplasm in the midpiece of the flagellum. Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme that stimulates the mitochondrial NADH-dependent oxido-reductase system, which subsequently leads to ROS production. There is also a concurrent leakage of electrons in
the mitochondrial electron transport chain (ETC), which leads to enhanced ROS production, primarily from Complex I or Complex III (Koppers, De luliis, Finnie, McLaughlin, & Aitken, 2008).

The number of leucocytes in the seminal plasma increases with genital tract infection and/or inflammation (i.e., epididymitis and prostatitis.). Peroxidase-positive leucocytes can produce approximately 1,000 times more ROS than spermatozoa by enhancing nicotinamide-adenine dinucleotide phosphate (NADPH) production via the hexose monophosphate shunt (Ford, Whittington, & Williams, 1997). ROS production must be in the normal physiological levels for homeostasis.

### 1.2 Causes of sperm DNA damage

During late spermatogenesis, downregulation of DNA repair systems exposes male germ cells to a higher probability of DNA damage. The cellular machinery that allows spermatozoa to undergo complete apoptosis is progressively lost during spermatogenesis. Additionally, abnormal spermatozoa originally earmarked for elimination are able to escape apoptosis (Lewis & Aitken, 2005). As a result, ejaculated spermatozoa show both nuclear and mitochondrial DNA damage (Sawyer, Roman, & Aitken, 2001; Sawyer et al., 2003). Spermatozoa are susceptible to OS because their plasma membrane contains an unusually high percentage of polyunsaturated fatty acids (PUFAs), which are susceptible to a damaging process called lipid peroxidation (reviewed in Agarwal, Saleh, & Bedaiwy, 2003). Lipid peroxidation occurs as electrons from plasma membrane lipids are stripped away by ROS. This propagates a chain of redox reactions that eventually generates highly mutagenic and genotoxic electrophilic aldehydes such as malondialdehyde (MDA), 4-hydroxynonenal (4-HNE) and acrolein (Luczaj & Skrzyliewska, 2003). 4-HNE is derived from lipid hydroperoxides of ω-6 fatty acids such as linoleic acid and arachidonic acid (Yin, Xu, & Porter, 2011). MDA forms primarily from the peroxidation of PUFAs with more than two methylene-interrupted double bonds such as arachidonic acid and docosahexaenoic acid (Esterbauer, Schaur, & Zollner, 1991). 4-HNE is the most genotoxic by-product, whereas MDA is the most mutagenic. 4-HNE and acrolein, in turn, induce a significant dose-dependent increase in lipid peroxidation, mitochondrial ROS production, DNA fragmentation and apoptosis (Aitken et al., 2012). Thus, the plasma membrane is a key target of ROS, which stimulates the cascade of events that damage the genetic composition of spermatozoa.

### 1.3 Types of DNA damage

DNA damage observed in spermatozoa is a result of OS. It is an important characteristic of semen quality and therefore a useful marker in the diagnosis of male infertility. Both OS and abnormal apoptosis are the major causes of DNA damage. OS is associated with reduced fertilisation, dysregulated pre-implantation development of the embryo, miscarriage, birth defects in the offspring and childhood cancer linked to paternal smoking (Bungum et al., 2012; Fraga, Motchnik, Wyrobek, Rempel, & Ames, 1996; Ji et al., 1997; Lewis & Aitken, 2005; Simon, Castillo, Oliva, & Lewis, 2011; Simon et al., 2014; Zini, 2009; Zini & Sigman, 2009).

DNA damage can result in a number of modifications such as (i) single- and double-strand breaks; (ii) DNA fragmentation; (iii) introduction of abasic sites; (iv) modifications in purine, pyrimidine and deoxyribose; and (v) DNA crosslinking (Aitken, Gibb, Baker, Drevet, & Gharagozloo, 2016; Singh & Agarwal, 2011; Singh et al., 2014; Zini, 2009; Zini & Sigman, 2009).

DNA damage can result in arrest or induction of gene transcription, induction of final transduction pathways, increased attrition of telomeric DNA, replication errors, genomic instability and transversions of GC to AT (Bauer, Corbett, & Doetsch, 2015; Hosen, Islam, Begum, Kabir, & Howlader, 2015; Li, Yang, & Huang, 2006).
DNA fragmentation is a typical endpoint of ROS-mediated damage and is most commonly observed in the spermatozoa of infertile men (Dorostghoal, Kazeminejad, Shahbazian, Pourmehdi, & Jabbari, 2017; reviewed in Bisht, Faiq, Tolahunase, & Dada, 2017b). These single-stranded or double-stranded fragments can occur either from direct or indirect ROS-mediated damage (See Figure 2).

ROS generate oxidised DNA base adducts within the DNA strand such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG)—a process which at the early stage is still reversible (reviewed in De luliis et al., 2009). Spermatozoa contain only one base excision repair enzyme upstream in the frame reading process. They are equipped with 8-oxoguanine DNA glycosylase (OGG1), which excises the base adduct out of the DNA sequence (Rosenquist, Zharkov, & Grollman, 1997). DNA integrity in spermatozoa is highly dependent on OGG1 activity (Guz et al., 2013).

OS is directly linked with oxidative modifications of DNA bases and can be measured by determining the levels of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodG) in spermatozoa. 8-OHdG is considered the hallmark of DNA damage as DNA fragmentation and cell death ensue (Aitken, De luliis, Finnie, Hedges, & McLachlan, 2010; Muratori et al., 2015). 8-OHdG has been associated with suboptimal fertility outcomes. Thus, efficient methods of detecting 8-OHdG are needed for clinicians to anticipate and treat clinical sequelae. Levels of 8-oxodG significantly correlate with sperm count, motility and morphology (Guz et al., 2013). Higher 8-oxodG levels are also reported in men with oligozoospermia, asthenozoospermia, oligoasthenozoospermia as well as cryptozoospermia compared to normozoospermic controls (Guz et al., 2013). As spermatozoa lack the downstream DNA repair proteins of the base excision repair pathway such as apurinic endonuclease 1 (APE1) and X-ray repair cross-complementing protein 1 (XRCC1), DNA fragmentation will most likely occur in the presence of direct oxidative insult (Smith et al., 2013).

1.4 Clinical significance

Although DNA damage is induced at low levels of OS, there are reports that fertilisation actually improves, which suggests the importance of the cellular redox status in events such as capacitation and hyperactivation associated with tyrosine phosphorylation (Aitken, Harkiss, Knox, Paterson, & Irvine, 1998; Aitken, Gordon, et al., 1998). The fertilisation potential of spermatozoa is severely disrupted at high levels of OS as a consequence of collateral peroxidative damage to the sperm plasma membrane (Aitken, Harkiss, et al., 1998). Furthermore, fertilised spermatozoa are capable of disrupting the epigenetic regulation of embryo development. However, this is true only in natural conception, intrauterine insemination (IUI) and in vitro fertilisation (IVF). This is not the case in intracytoplasmic sperm injection (ICSI) where all the functional processes associated with natural conception such as capacitation, acrosome reaction, binding, fusion and penetration of the zona pellucida are bypassed (Aitken & Baker, 2004; Lewis, O’Connell, Stevenson, Thompson-Cree, & McClure, 2004). Post-fertilisation development of the embryo can be seriously disrupted by abnormal chromatin packaging and DNA damage which can result in reduced rates of embryo cleavage and pregnancy.

Moderate to high levels of sperm DNA damage are reported in over 60% of patients (Cohen-Bacrie et al., 2009). Despite the potential risks, the impact of DNA damage and its clinical significance remains controversial (Drobnis, 2015; Lewis, 2015, Practice Committee of American Society for Reproductive Medicine, 2008; Practice Committee of the American Society for Reproductive Medicine, 2013). This is largely attributed to (i) nonstandardised assays to detect DNA damage; (ii) studies with small sample size and/or inadequate study design and ability of the oocyte to repair the DNA; (iii) lack of clinical studies that consistently demonstrate the
Mechanism of ROS-mediated mitochondrial DNA damage. A cyclic cascade of oxidative stress is generated from mitochondrial dysfunction. IMM, inner mitochondrial membrane; mtDNA, mitochondrial DNA; ETC., electron transport chain.

FIGURE 3

Abnormal ROS generation
Concurrent leakage of electrons from ETC
IMM compromised
mtDNA damaged directly

A small circular DNA located inside mitochondria and is encoding for 37 genes in the human. mtDNA plays a crucial role in oxidative phosphorylation and ATP generation. Additionally, it encodes for the 13 polypeptides of the ETC. complexes which are necessary for spermatogenesis and sperm motility (reviewed in Amaral, Lourenco, Marques, & Ramalho-Santos, 2013). ROS generation in the mitochondria that originates from functionally defective spermatozoa can attack sperm DNA and affect the physiological functions of the spermatozoa (Aitken & De Iuliis, 2010; Gil-Guzman et al., 2001; Gomez et al., 1996; Koppers et al., 2008).

mtDNA is 100 times more susceptible to genetic mutations when compared to nuclear DNA. This is because of its inherent circular structure with few DNA base pairs, absence of histones and lack of nucleotide excision repair pathways (Sawyer et al., 2003; Shamsi et al., 2008). Furthermore, mtDNA mutation rate is two-fold higher than that of nuclear DNA. Spermatozoa with a larger number of damaged mitochondria cannot undergo complete apoptosis and may result in a larger number of ejaculated spermatozoa that have damaged DNA (Shamsi et al., 2008). Increased ROS production and lower ATP levels are seen in spermatozoa with mutated mitochondria. Subsequent increased mitochondrial copy number may lead to hypospermatogenesis due to meiotic arrest during sperm development and/or a disorganised axonemal complex as evidenced by asthenozoospermia (Feng, Song, Zou, & Mao, 2008). Additionally, in patients with asthenozoospermia, spermatozoa show significant increase in mtDNA copy number when compared to that of controls (Bonanno et al., 2016). Normally, there is minimal contribution of paternal mtDNA to the genome of an embryo as it is quickly eliminated in early embryonic development (May-Panloup et al., 2003; reviewed in Benkhalifa et al., 2014). This suggests that defective spermatozoa have the potential of transmitting abnormal paternal mtDNA. Interestingly, a number of genetic defects in the ETC. complexes with coexisting elevations of MDA have been identified in oligozoospermic men (Kumar et al., 2009). This suggests that dysfunctional mitochondria accelerate OS by increasing ROS production and inducing lipid peroxidation. This vicious cycle of enhanced ROS production causes extensive damage (See Figure 3: Henkel, 2010).

Lastly, OS-induced mutations in OGG1 significantly reduce the ability of OGG1 to excise DNA base adducts. Animal studies have shown that repair of 8-oxodG is regulated differently in nucleus and mitochondria during the ageing process. Furthermore, specific increase in 8-oxodG-incision activity in mitochondria, rather than a general upregulation of DNA metabolising enzymes in those organelles, suggests that this pathway may be upregulated with advanced age (de Souza-Pinto, Hogue, & Bohr, 2001). Throughout life, men produce spermatozoa that will accumulate OS-induced DNA damage. The integrity of the genetic code is compromised due to an increased number of cell divisions, defective DNA replication fidelity, inefficient DNA repair and accumulations of mutations both from internal and external sources. Overall, it is important for clinicians to not overlook mtDNA damage as it can result in increased

significance of OS in the diagnosis of male infertility; and (iv) conflicting data regarding type of antioxidants, their concentration and duration of antioxidants required in the management of the disease. All of these factors reflect the complexity of the reproductive system.

1.5 | Apoptosis

Apoptosis is a separate mechanism that leads to DNA fragmentation as it is characterised by a disassembly of chromatid during programmed cell death. This natural process plays a vital role in facilitating appropriate germ cell development and maintaining the germ cell-Sertoli ratio in the testis (Rodriguez, Ody, Araki, Garcia, & Vassalli, 1997). High levels of ROS cause a heightened and dysregulated apoptotic response (Aitken & Baker, 2013). Elevated caspase levels, specifically caspase 3 and caspase 9, as well as increased phosphatidylserine externalisation has been reported in the ejaculate of infertile men (Agarwal et al., 2003; Almeida, Sousa, & Borros, 2009). Dysregulation of apoptosis is exemplified in a phenomenon called abortive apoptosis, where a higher percentage of Fas-positive spermatozoa was observed in men with abnormal semen parameters (Sakkas, Mariethoz, & St John, 1999).

1.5.1 | Clinical significance

Nonregulated apoptosis poses a great threat to reproduction as spermatozoa with fragmented DNA are able to mature and fertilize an oocyte (Aitken, Gordon, et al., 1998). Apoptosis-related sperm DNA damage, if carried into the zygote at the time of fertilization, must be repaired before the first cleavage division. If this damage is not repaired, it has the potential to induce mutations which can impact the development, health and well-being of the child (Aitken & Krausz, 2001).

1.6 | Mitochondrial DNA damage

There are approximately 70–80 mitochondria per spermatozoa in the midpiece of the flagellum. Mitochondrial DNA (mtDNA) is

increase in 8-oxodG-incision activity in mitochondria, rather than a general upregulation of DNA metabolising enzymes in those organelles, suggests that this pathway may be upregulated with advanced age (de Souza-Pinto, Hogue, & Bohr, 2001). Throughout life, men produce spermatozoa that will accumulate OS-induced DNA damage. The integrity of the genetic code is compromised due to an increased number of cell divisions, defective DNA replication fidelity, inefficient DNA repair and accumulations of mutations both from internal and external sources. Overall, it is important for clinicians to not overlook mtDNA damage as it can result in increased
OS, impaired spermatogenesis and asthenozoospermia. Assessment of mitochondrial integrity may be a sensitive method for evaluating human spermatozoa function.

### 1.6.1 Clinical significance

Increased addition of mtDNA fragments into nuclear genome can also trigger activation of oncogenes which can increase the risk of gonadal and extragonadal tumours (Turner, & Hartshorne, 2003; Venkatesh, Deecaraman, Kumar, Shamsi, & Dada, 2009; Venkatesh, Shamsi, et al., 2011).

### 1.7 Telomere attrition

Telomeres are cap-like structures present at the end of the chromosomes essential for maintaining normal genomic structure. They are noncoding, repeating DNA sequences (5’-TTAGGG-3’) that protect the ends of chromosomes from being recognised as DNA breaks and subsequently degraded. Furthermore, telomeres are likely targets of ROS due to their rich guanine structure and low oxidation potential (Guz et al., 2013; Klungland & Bjelland, 2007). Similar to the mechanism of DNA fragmentation, ROS generate highly mutagenic DNA base adducts, resulting in both single- and double-strand DNA breaks (De luliis et al., 2009) and accelerated telomere attrition (Kawanishi & Oikawa, 2004; Ma, Zhu, Hu, Yu, & Yang, 2013; Wang et al., 2010). With each cell division, end-replication problems result in the loss of most distal telomere repeats.

Excessive telomere shortening seen after repeated cell divisions leads to end–end fusions, cell arrest and apoptotic DNA fragmentation that is accelerated by OS (Artandi & DePinho, 2000; Blasco, 2003). Essentially, this is a safeguard to prevent consequences of telomerase dysfunction such as ageing and the development of cancer (Artandi & DePinho, 2000; Blasco, 2003). If telomere attrition is left unchecked, OS will trigger replicative senescence and proliferation arrest. Therefore, telomeres serve as a mitotic clock. Telomeres are shorter in men compared with those of women due to a higher age-dependent rate of attrition (Mayer et al., 2006; Thilagavathi, Venkatesh, & Dada, 2013).

New telomeric repeats are synthesised by the catalytic subunit of telomerase—telomerase reverse transcriptase (TERT)—and an RNA molecule (TERC) (Rodríguez et al., 2005). In animal studies, critically short telomeres have been associated with sperm DNA fragmentation (Rodríguez et al., 2005). Specifically, in mammalian male germ line cells, TERT helps with proper spermatogenesis. In infertile men, TERT activity was low as shown through histological testicular samples (Fujisawa et al., 1998). ROS indirectly damage telomeres by attenuating TERT activity, a feature that is necessary to maintain telomere length (Haendeler et al., 2004; Zhu, Fu, & Mattson, 2000) (See Figure 4). Telomeric sequences are lost in the absence of telomerase after each round of DNA replication.

### 1.7.1 Clinical significance

Studies have also shown that male telomeres may be the first structures to initiate pronucleus formation—a process vital to fertilisation (Zalenskaya, Bradbury, & Zalensky, 2000). As a result, telomere attrition has been associated with cytoplasmic fragmentation, abnormal cleavage, chromosomal aneuploidy and poor embryonic development (Burruel, Klooster, Barker, Pera, & Meyers, 2014; Liu, Blasco, Trimarchi, & Keefe, 2002). Sperm telomere length is also associated with both semen quality and DNA integrity. Thus, enhanced telomere attrition may lead to cellular ageing and senescence (reviewed in Bernadotte, Mikhelson, & Spivak, 2016). Specifically, ROS-mediated telomere attrition can cause testicular ageing and hypospermatogenesis. Men with oligozoospermia have shorter sperm telomeres compared to those of normozoospermic men (Ferlin et al., 2013). Interestingly, however, mild OS is essential for the maintenance of telomere length (Aitken, Harkiss, et al., 1998; Mishra, Kumar, Malhotra, Singh, & Dada, 2016).

Telomere length is one of the important factors involved in impaired reproduction and in limiting lifespan, particularly at the cellular level. This is because it functions as a biological clock. Although telomere length is partially determined genetically and by paternal age, it is also influenced by internal and external environmental factors such as obesity, infection, oxidative stress, smoking, psychological and lifestyle stress, environmental factors and diet (Thilagavathi et al., 2013). However, currently, analysing sperm telomere length is not a part of standard clinical practice due to some conflicting data surrounding its relationship with sperm DNA fragmentation, sperm parameters and reproductive outcomes (Cariati et al., 2016; Lafuente et al., 2017;
Rocca et al., 2016; Turner & Hartshorne, 2013; WHO, 2010). Thus, the validity of telomere length as a diagnostic tool of infertility and OS has yet to be confirmed.

1.8 | Epigenetic abnormalities

Epigenetics is the study of changes that occur in gene expression as a result of modifications of nuclear chromatin or covalent modifications of bases associated with DNA. These modifications result in changes in the phenotype without any alteration in genotype. Epigenetics mechanisms, such as DNA methylation, are essential for proper gene expression and cellular differentiation (Jones & Taylor, 1980). The role of ROS in epigenetics and its impact on male infertility is a fairly new field of study. Methylation of the cytosine residues in DNA occurs by methyltransferase enzymes. In mice, male germ cells lacking DNA methyltransferase 3-like (Dnmt3L) activity exhibited incomplete gametogenesis and gamete maturation (Bourc'his & Bestor, 2004; Kaneda et al., 2004; Oakes, La Salle, Smiraglia, Robaire, & Trasler, 2007). Similarly, in humans, ROS-mediated global hypomethylation has been associated with Sertoli cell-only syndrome, testicular cancers and hypospermatogenesis (Faure et al., 2003; Olszewska et al., 2017; Tunc & Tremellen, 2009; Urdinguio et al., 2015). Histone acetylation, another vital mechanism for epigenetic changes, may also be dysregulated in the conditions aforementioned. Further research is needed to understand the mechanisms of ROS-mediated damage on epigenetics.

1.9 | Y chromosome microdeletions

The Y chromosome-specific genes encode molecules that are essential for sex determination or male fertility. Y chromosome microdeletions and elevations of ROS have been observed in infertile men (Shamsi, Dada, & Dinesh, 2012; Venkatesh, Thilagavathi, et al., 2011). Y chromosomes are very susceptible to gene deletions because the haploid genome is unable to position recombination repair and is unable to retrieve the lost genetic information (Aitken & Krausz, 2001). There are multiple factors responsible for Y chromosome deletions on the spermatozoa. Such examples include aberrant recombination, defective chromatin packaging, abortive apoptosis and OS experienced during the differentiation and maturation processes in the male reproductive tract. Normally, double-stranded DNA breaks would be repaired by homologous recombination shortly at the time between fertilisation and initiation of the first cleavage division. Recombination is impossible in the nonrecombining regions of the Y chromosome, which houses the key spermatogenesis genes. When DNA damage is excessive, the genes on the long arm of the Y chromosome will induce infertility. This is a safety mechanism that limits the extent to which mutations can be propagated in the germ line (Aitken & Krausz, 2001).

1.9.1 | Clinical significance

Gene deletion in the Y chromosome region is seen in about 15% of patients with azoospermia and about 5%–10% of subjects with severe oligozoospermia. Azoospermia factor (AZF) region is highly implicated in male infertility. Y chromosome microdeletions follow the deletion pattern of three recurrently deleted nonoverlapping subregions that are located in the proximal, middle and distal Yq11 subregion and designated AZFa, AZGb and AZFc respectively. Deletions of the entire AZFa region will result in type I Sertoli cell-only syndrome (SCOS) or complete absence of germ cells. Deletions of the AZFb region result in spermatogenic arrest mostly at the spermatocyte stage only. Deletions of the AZFc region are associated with hypospermatogenesis resulting in oligozoospermia with type II SCOS presenting with spermatogonia.

1.10 | Antioxidant use for male infertility

Recent scientific evidence encourages antioxidant administration for the treatment of OS-mediated male infertility. Antioxidants have been shown to improve semen parameters and reproductive outcomes (Asadi, Bahmani, Kheradmand, & Rafieian-Kopaei, 2017; Gaskins & Chavarro, 2017; Majzoub & Agarwal, 2017; Salas-Huetos, Bullo, & Salas-Salvado, 2017). Antioxidants, either obtained naturally through food or vitamin supplements, help neutralise free radicals that contribute to seminal OS. Antioxidant compounds showing promise include glutathione, vitamin E, vitamin C, carnitines, coenzyme Q10, N-acetyl cysteine, selenium, zinc, folic acid and lycopene. It is important to strictly adhere to the suggested daily dosages in order to avoid overdosage as this can shift the fine balance between oxidation and reduction to a state called “reductive stress”, which is as dangerous as OS (Castagne, Lefevre, Natero, Clarke, & Bedker, 1999). In addition, there is evidence that well-known antioxidants such a vitamin C exhibit pro-oxidant effects if they are given in an overdose; a chemical behaviour which is called the “antioxidant paradox” (Halliwell, 2000, 2013; Majzoub & Agarwal, 2017). Supratherapeutic levels of antioxidants can inhibit the activation of transcription factors essential for sperm capacitation, hyperactivation and acrosomal reaction (Du Plessis, Agarwal, Halabi, & Tvrdá, 2015; Henkel, 2011). Additionally, physiological OS-induced apoptosis may be inhibited which allows for the survival of defective cells (Halliwell, 2000). Overall, in order to optimise reproductive success, it is important to maintain a balance between the oxidative and reductive factors in the body.

2 | CONCLUSION

ROS causes OS that results in DNA damage which is evident in multiple forms such as DNA fragmentation, mitochondrial DNA damage leading to telomere attrition, epigenetic abnormalities and Y chromosome microdeletions. Thus, the clinical consequences of OS and DNA damage are detrimental and contribute to the worldwide burden of male infertility. Identifying the source of oxidative stress and adopting appropriate management and therapeutic strategies are essential to minimising oxidative insult, improving sperm quality and increasing the chances of a successful pregnancy.
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COMPETING INTERESTS

None of the authors declare competing financial interests.

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