Environmental Toxicants and Male Reproductive Toxicity: Oxidation-Reduction Potential as a New Marker of Oxidative Stress in Infertile Men

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Abstract Exposure to various environmental and lifestyle-dependent factors such as heavy and trace metals, hydrocarbons, ethylene glycol ethers, obesity, tobacco, alcohol and recreational drugs etc. have been identified to cause reproductive toxicity in men. A number of toxicants affect spermatogenesis leading to poor semen quality affecting fertility in such men, primarily through the mechanism of oxidative stress. In the male reproductive system, oxidative stress is brought about either by excessive production of extrinsic free radicals or by reduced activity of intrinsic antioxidants thereby disrupting the redox balance. Discrete measures of reactive oxygen species, total antioxidant capacity, and post hoc damage suggest an ambiguous relationship between the redox system and male fertility. Antioxidants work by donating electrons to the oxidants, thereby reducing the chances of oxidants to acquire electrons from other nearby structures and cause oxidative damage. Oxidation-reduction potential (ORP) measures this relationship between oxidants and antioxidants in semen. The MiOXSYS system used to measure ORP requires a small volume (~30 μl) of liquefied semen and the measurement is completed in less than 5 min. The galvanostat-based analyzer uses electrochemical technology to measure the ORP in millivolts (mV) which is then normalized to express as $mV/10^6$ sperm/mL. The role of ORP as a surrogate marker to conventional semen quality parameters is a current topic of investigation by a number of researchers and clinicians. It can be measured in semen and seminal plasma up to 2 h of liquefaction. ORP correlates negatively with conventional as well as advanced semen quality parameters, including sperm concentration, total sperm count, total motile sperm count, motility, morphology, and DNA fragmentation thus confirming the association of oxidative stress with male factor infertility. ORP values can differentiate the degree of oxidative stress-induced male

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infertility. A number of clinical studies involving cohorts of men from USA, Qatar and India have established seminal ORP cut-off values to distinguish fertile men from infertile patients. Monitoring ORP levels may help predict treatment efficacy in patients as higher ORP values are indicative of the progression of infertility. It can also be measured in cryopreserved semen samples, which is important in predicting the success of assisted reproductive techniques (ART). A recent ART study reported higher clinical pregnancy rate in infertile men with low seminal ORP in comparison to patients with high ORP. Findings of recent clinical investigations indicate ORP as a novel, independent and robust diagnostic marker of seminal oxidative stress that should find its place in the male infertility workup algorithm.

Keywords Environment · Lifestyle · Toxicity · Semen · Male reproduction · Infertility · Oxidative stress · Oxidation-reduction potential

1 Introduction

Reproduction is a natural process for most of the couples involving neither special planning nor intervention. However, 15% of couples struggle to conceive after one year of regular, unprotected intercourse and, consequently, seek medical advice on how to improve their chances of fertilization and successful pregnancy (Trussell 2013). Hence, infertility has become the most important public health concern affecting 48.50 million couples globally (Agarwal et al. 2015a, b) wherein only the male factor accounts for 40–50% of infertility cases (Kumar and Singh 2015). Several toxicants of chemical and physical origin generated by industrial and agricultural activities are released into the environment constitute a putative hazard to the fertility of men (Spira and Multigner 1998). Exposure to various environmental and lifestyle-dependent factors have been associated with excessive production of extrinsic free radicals or reduced activity of intrinsic antioxidants thereby causing oxidative stress in the male reproductive system that may gradually manifest into reproductive toxicity affecting fertility in such men (Jana and Sen 2012; Pizent et al. 2012; Aitken et al. 2014; Gabrielsen and Tanrikut 2016). Clinicians largely rely on routine semen analysis for the diagnosis of male infertility in spite of poor association of conventional semen parameters with male fertility potential (Björndahl et al. 2015; Agarwal et al. 2017a). However, it is felt by many clinicians as well as researchers that male fertility evaluation should not be based on conventional semen analysis alone and more reliable, quantifiable, unbiased and universal functional measures of semen quality must be incorporated in male infertility evaluation (Esteves 2014; Agarwal et al. 2017a).

2 Environmental Toxicants and Male Reproductive Functions

A number of environmental toxicants have been identified to affect spermatogenesis leading to low sperm count, abnormal sperm morphology and eventually poor semen quality. Various classes of compounds such as heavy metals, organic polychlorinated dibenzodioxins, dicarboximide fungicides, environmental phenols and several other different classes of pollutants and chemicals are often released into the environment during industrial processes which are gradually taken up by humans through the ingestion of contaminated food and water, usage of consumer products (e.g. plasticware and cosmetics etc.), inhalation of polluted air and so on (Spira and Multigner 1998; Aitken et al. 2004; Sharpe 2010).

2.1 Heavy and Trace Metals

Plethora of evidences revealed negative impact of heavy metals including cadmium, lead, manganese, chromium, copper, mercury, nickel and silver on male infertility. Significantly higher levels of cadmium was reported in blood and seminal plasma of infertile patients in comparison to fertile men or men from the normal population upon environmental exposure which was further validated in animal model and reduced sperm concentration and motility was noted (Benoff et al. 2009). Seminal plasma cadmium level was found to be significantly higher than the serum cadmium level when it was tested among 60 infertile males and 40 normozoospermic subjects (Akinloye et al. 2006). Application of low dose of cadmium was able to disrupt inter-Sertoli cell tight junctions in rats leading to disruption of spermatogenesis (Siu et al. 2009). Cadmium also contributes to infertility in males with varicoceles as the percentage of apoptotic nuclei and testicular cadmium levels were found to be high in such men (Benoff et al. 2004). Lead is another heavy metal that passes to the bloodstream and is incorporated into the tissues, including hypothalamus, hypophysis, and testes due to ingestion or inhalation, affecting neuroendocrine system (Lamb and Bennett 1994). Reduced sperm cell formation was observed in 150 workers exposed to lead in their workplaces (Lancranjan et al. 1975). High lead concentration in blood was also noted among people working in batteries and paint factories with decreased sperm velocity, reduced sperm motility suggesting retarded sperm activity (Lamb and Bennett 1994; Naha and Chowdhury 2006). Literatures revealed that manganese could alter reproductive functions, elevated levels exhibiting harmful effects on sperm morphology and motility (Li et al. 2012). Copper, an essential trace metal, can decrease sperm function including concentration, viability and motility in mammalian model in its ionic and non-ionic forms in a dose-dependent and time-dependent manner indicating the possibility of its adverse affect on male fertility (Holland and White 1988; Roychoudhury and Massanyi 2008; Roychoudhury et al. 2010, 2016a, b). Molybdenum concentration was found to be the most consistent in

blood with reduced sperm concentration and morphology when a bunch of essential and nonessential metals (arsenic, cadmium, chromium, copper, lead, manganese, mercury, molybdenum, selenium and zinc) were subjected to assess their effects on semen quality (Meeker et al. 2008).

2.2 Pollutants

Several pollutants are associated with deteriorating seminal quality depending upon the dose and time of exposure. Workers in tollgates were found to have lower sperm motility including lower progressive motility and sperm kinetics than the control males (Rosa et al. 2003). Hydrocarbons such as toluene, benzene and xylene were reported in the blood and semen of some workers at workplaces where their air concentration exceeded the maximum permissible levels resulting in decreased sperm vitality and motility in the occupationally exposed men (Xiao et al. 2001). Adverse effect of dioxin exposure during infancy or at puberty was associated with reduction in sperm concentration, progressive motility, total motile sperm count, estradiol and an increase in follicle stimulating hormone (Mocarelli et al. 2008). It is also believed that environmental pesticide exposures can adversely affect spermatogenesis in men at large. Environmental exposures to polychlorinated biphenyls (PCB) and dichlorodiphenyldichloroethylene (DDE) were found to be associated with altered semen quality parameters when a cross-sectional study was conducted on 212 male partners of subfertile couples (Hauser et al. 2003).

2.3 Chemicals

Plethora of evidence reflects the pronounced adverse effect of chemical exposures during adulthood affecting testicular and post-testicular functions and male fertility. For instance, ethylene glycol ethers produced by chemical industry (especially, ethylene glycol methyl ether and ethylene glycol ethyl ether) exerts deleterious effects on reproduction and fertility in mammalian models (Boatman 2001; Multigner et al. 2005). In a human study, exposure to glycol ether was linked to a secular decrease in semen quality (Multigner et al. 2007). Another common industrial chemical exhaust, bisphenol A (BPA) has been associated with lowered sperm count and motility in men who worked in the BPA-based factories (Rahman et al. 2015; Manguez-Alarcon et al. 2016).

3 Lifestyle and Male Reproductive Functions

There are some lifestyle-dependent factors including obesity, smoking, alcohol and drugs that play a vital role in male reproductive health. However, these factors reflect less conclusive evidences affecting semen quality and male fertility.

3.1 Obesity

Obesity is an important lifestyle-dependant factor that has negative impact on spermatogenesis and/or male fertility. Evidences suggest that men with poor semen quality are three times more likely to be obese than men with normal semen quality. Male infertility was found to be associated with a higher incidence of obesity exhibiting reduced androgen levels and sex hormone-binding globulin levels accompanied by elevated estrogen levels, thereby indicating endocrine dysregulation in obese men and increased risk of altered semen parameters and infertility (Magnusdottir et al. 2005; Hammoud et al. 2008). In overweight and obese men (BMI $\geq$ 25 kg/m^2) mean sperm concentration was found to be lower than those of normal-weight men (BMI 20–25 kg/m^2) (Jensen et al. 2004). Obesity was also associated with a 1.3-fold relative risk for erectile dysfunction which can be explained by the decreased T levels and elevated levels of several pro-inflammatory cytokines in such individuals (Bacon et al. 2003; Seftel 2006).

3.2 Smoking and Alcohol

Cigarette smoking and alcohol consumption are two major recreational factors that usually come top of the list of affecting male reproductive health. Sperm density was reported to be much lower among smokers in comparison to non-smokers (Vine et al. 1996). Among smokers, reduced sperm density, decreased total sperm count and lower total number of motile sperm was observed, too (Kunzle et al. 2003). Another study strongly associated tobacco chewing males in India with a decrease in their semen quality and the extent of oligoasthenozoospermia or azoospermia (Said et al. 2005). Smoking was believed to be the cause of seminal oxidative stress, lack of sperm plasma membrane integrity and DNA fragmentation that directly corroborate with male infertility (Saleh et al. 2002; Belcheva et al. 2004; Sepaniak et al. 2006). Alcohol consumption has been associated with impairment of spermatogenesis and reduction in sperm counts and testosterone levels (Muthusami and Chinnaswamy 2005). A significant decrease in the number of sperm cells was noted due to severe alcohol intake (Donnelly et al. 1999; La Vignera et al. 2013). A synergistic effect of cigarette smoking and alcohol consumption results in significant reduction of seminal volume,

sperm concentration, percentage of motile spermatozoa, and increased number of non-motile viable gametes (Martini et al. 2004; Guthauser et al. 2013).

3.3 Recreational Drugs

A few studies demonstrated the adverse impact of recreational drugs such as cocaine, cannabis and marijuana on male infertility although the actual mechanism is not very clear. Use of cocaine for five or more years was found to be associated with lower sperm motility, concentration and abnormal morphology (Bracken et al. 1990). Similar results were also observed in chronic use of marijuana (Harclerode 1984). Deleterious effects of delta-9-tetrahydrocannabinol, the active compound of marijuana on sperm function was evident from the reduction in sperm progressive motility and decreased acrosome reaction (Whan et al. 2006). In addition, methadone and heroin were found to cause lower serum testosterone concentrations, reduced sperm motility, lower ejaculate volumes and abnormal sexual dysfunction (Fronczak et al. 2012). Use of anabolic androgen steroids by athletes, weightlifters and bodybuilders induces a state of hypogonadotrophic hypogonadism by means of decreasing testosterone concentration thereby reducing spermatogenesis (Knuth et al. 1989; Karila et al. 2004). Interestingly, a few prescribed drugs of different types may also exert adverse impact on spermatogenesis. For instance, sulfasalazine, used for the treatment of irritable bowel disorders and some other chemotherapeutic agents (e.g. cyclophosphamide) used for treatment of cancers or kidney diseases may induce infertility in men (Nudell et al. 2002; Feagins and Kane 2009; Semet et al. 2017).

4 Oxidative Stress, Male Reproductive Toxicity and Infertility

Reactive oxygen species (ROS) are molecules that contain an oxygen atom with an unpaired electron in outer shell. Due to the unpaired electron in the outermost shell they become very unstable and these unstable forms of oxygen are called free radicals. ROS are produced in living cells either from intrinsic or extrinsic sources as byproducts of cellular metabolism resulting from mitochondrial respiration through oxidative phosphorylation (Sharma and Agarwal 1996; Dickinson and Chang 2011; Chen et al. 2003; Lavranos et al. 2012; Roychoudhury et al. 2017a, b). ROS hinder the cells' own natural antioxidant defense system. Endogenous antioxidants or those acquired from diet limit the damage to cells by detoxifying these reactive intermediates by donating an electron to ROS to stabilize them (Finkel 2011). Under normal physiological circumstances ROS are present in genital tract in low concentration (Guerin et al. 2001; Roychoudhury et al. 2017a, b) which is necessary for functions of the male gamete including capacitation, hyperactivation and acrosome reaction

(Aitken and Fisher 1994; Sharma and Agarwal 1996). Oxidative stress occurs when the delicate balance in the redox system that maintains equilibrium between the ROS and the antioxidants, is disturbed (Agarwal et al. 2017a; Roychoudhury et al. 2017a, b). Studies indicated that infertile men are more likely to have higher concentrations of ROS and lower level of antioxidants in their seminal plasma (de Lamirande and Gagnon 1995; Roychoudhury et al. 2016a, b). ROS causes reproductive toxicity and impairs fertility by means of two principal mechanisms. First, being rich in polyunsaturated fatty acids, sperm cell membranes are highly vulnerable to ROS; thereby lipid peroxidation of the plasma membrane takes place which in turn reduces sperm motility, quality and fertility (Henkel 2011; Aitken et al. 2014, 2016). Secondly, ROS directly damage sperm DNA affecting the purine and pyrimidine bases and the deoxyribose backbone (Agarwal et al. 2003; Oliva 2006). Additionally, ROS may initiate apoptosis within the sperm, leading to caspase-mediated enzymatic degradation of the sperm DNA (Moustafa et al. 2004; Villegas et al. 2005). Leukocytes especially neutrophils and macrophages, as well as immature spermatozoa include the major endogenous sources of ROS. Environmental and lifestyle factors discussed earlier in this chapter play an important role in production of exogenous ROS leading to male reproductive toxicity and infertility which have been confirmed by studies in human subjects as well as mammalian models (Saleh et al. 2003; Gharagozloo and Aitken 2011).

Amongst several environmental factors mentioned above, cadmium directly induces oxidative stress in testes affecting sperm production, testosterone activity, secretion, spermatogenesis impairment as well as it decreases antioxidant defense system by means of reducing superoxide oxidase, glutathione peroxidase and catalase enzyme activity of seminal plasma membrane (Turner and Lysiak 2008; Sarkar et al. 2013). Testicular cadmium level has been associated with varicocele which is the most common correctable cause of male infertility and oxidative stress appears to be the primary mechanism of varicocele-induced injury (Benoff et al. 2004; Jensen et al. 2017). Lead exposure associated with oxidative stress contributes to an imbalance in the reproductive system disrupting testicular steroidogenesis by inhibiting the activities of testicular steroidogenic enzymes (Liu et al. 2008). Lead toxicity is also manifested by its deposition in testes, epididymis, vas deferens, seminal vesicle and seminal ejaculate which in turn reduce the sperm count, motility and germ cell population (Adhikari et al. 2001; Chowdhury 2009). Copper facilitates the production of superoxide radicals, hydroxyl radicals and hydrogen peroxide via the Haber-Weiss reaction causing oxidative damage and initiate adverse effect on spermatozoa concentration, viability and motility in animal models including reproductive toxicity of copper oxide nanoparticles (Roychoudhury and Massanyi 2008; Roychoudhury et al. 2010, 2016a, b). Manganese, required as a cofactor in many cellular enzymes including arginase, superoxide dismutase, alkaline phosphatase etc. has become a global concern due to its increased release into the environment which in turn accumulates in mitochondria, disrupting oxidative phosphorylation and increases the generation of ROS (Gunter et al. 2006). Manganese intoxication has been reported to lower synthesis and secretion of testosterone by acting directly on the Leydig cells or indirectly by acting on the anterior pituitary gland inhibiting the secretion of luteinizing

hormone which in turn inhibits androgen biosynthesis in Leydig cells (Chandel and Jain 2017).

Formaldehyde, a ubiquitous environmental pollutant, exerts detrimental effects on the reproduction, respiratory and haematological systems by means of production of excessive ROS (Zhou et al. 2006). Studies revealed that use of formaldehyde can lead to testicular atrophy and decreased testes weight, diameter of seminiferous tubules, seminiferous epithelial height and decreased number of spermatozoids (Golalipour et al. 2007; Gules and Eren 2010). Inhalation of toluene alters the hormonal status of the anterior pituitary gland in rodents as well as it facilitates oxidative damage to DNA and reproductive toxicity by means of decreased sperm number and increased 8-oxo-2′-deoxyguanosine formation in sperm cells of the testis (Nakai et al. 2003). Similarly, toxicity of benzene may result from oxidative metabolism of benzene to reactive products which ultimately cause DNA damage and this could be the possible mechanism by which benzene acts as a toxicant for spermatogenesis (Song et al. 2005). Long term exposure to xylene leads to reproductive toxicity through decreased spermatozoa viability, decreased motility with lower acrosin action from spermatozoa (Xiao et al. 2001). Polychlorinated biphenyls are the most environmentally persistent pollutants that disrupt the endocrine system (Apostoli et al. 2003) by reducing testosterone synthesis and steroidogenic enzyme activity in Leydig as well as Sertoli cells (Fiandanese et al. 2016), while ROS-induced BPA concentration is negatively associated with sperm concentration, normal morphology, and sperm DNA damage (Meeker et al. 2011). Administration of ethylene glycol monoethyl ether was found to be adversely affect steroidogenesis in rodents by decreasing the expression of steroid acute regulatory protein and androgen-binding protein (Adedara and Farombi 2013).

Furthermore, lifestyle-depended factors, such as obesity has been shown to be associated with the production of ROS which results in decreased sperm density and total count and significant negative correlation to increasing body mass index dysregulating the action of hypothalamic-pituitary-gonadal axis (Furukawa et al. 2004). Smoking and marijuana inhalation have been the key factors in the production of excessive ROS, which help in pathogenesis of several diseases including reproductive toxicity thereby inhibiting sperm motility, viability and thus fertility of the male (Close et al. 1990; Whan et al. 2006; La Maestra et al. 2015). On the other hand, although tobacco chewing is comparatively less harmful than smoking, it is not harmless altogether. It increases the risk of multiple oral premalignant lesions and affects semen parameters in a dose-dependent manner including reduced sperm concentration, motility, morphology, and viability (Said et al. 2005; Sunanda et al. 2014). However, the actual mechanism is still not known.

From the above discussion, it is clear that several environmental as well as lifestyle-dependent factors are involved in the pathophysiology of male infertility by means of mechanisms including oxidative stress-induced reproductive toxicity. Excessive increase in the generation of ROS and/or excessive decrease in the level of antioxidants may disrupt the seminal redox balance and trigger molecular changes that induce deterioration of semen quality and associated male fertility parameters including oxidative damage to sperm DNA, lipids and proteins. Therefore, allevia-

tion of oxidative stress constitutes a potential treatment strategy for male infertility (Agarwal et al. 2017a). Various direct and indirect tests used by different laboratories for measurement of seminal oxidative stress are discussed below.

5 Measurement of Oxidative Stress in Semen

Seminal oxidative stress is commonly measured by means of quantifying the ROS via chemiluminescence assay or by measuring the total antioxidant capacity (TAC assay) or post hoc damage by malondialdehyde (MDA) assay. The chemiluminescent ROS assay is based on the reaction between luminol and oxidizing compounds distinguishing poor quality of semen samples from good quality ones (Agarwal et al. 2014a, 2015a, b). The TAC assay is based on the ability of antioxidants present in semen to scavenge the ROS through specific or non-specific mechanisms (Muller et al. 2013). Amongst several TAC assays, Trolox equivalent antioxidant capacity is the most widely accepted test for determining seminal TAC levels between poor and good quality semen samples in order to differentiate infertile men from healthy ones (Roychoudhury et al. 2016a, b). The MDA assay determines the damage done to proximate lipids by free radicals in semen samples (Marnett 1999). However, these conventional approaches are single marker measurements that fail to capture both of the components of oxidative stress i.e. oxidants, and antioxidants/reductants (Agarwal et al. 2015a, b, 2017a). All of these have their own drawbacks as such assays are tedious, time consuming, involve sophisticated instruments and/or require special technical skills and large semen volumes causing difficulty in providing the full picture of the true oxidative state of the sample. Hence, a comprehensive measure of the activity of all known as well as unknown oxidants and antioxidants in a semen sample will better describe the state of the redox system thus facilitating better diagnosis and treatment of male infertility by the clinician.

6 Oxidation-Reduction Potential of Semen: A New Diagnostic Marker in Male Infertility

Antioxidants work by donating electrons to the oxidants, thereby reducing the chances of oxidants to acquire electrons from other nearby structures and cause oxidative damage. Oxidation-reduction potential (ORP) measures this relationship between oxidants and antioxidants in fluids including semen. Validation of a novel ORP diagnostic platform by comparison to mass spectrometry using disposable electrodes has paved the way for a rapid and comprehensive status of redox state in a sample. The difference between oxidants and antioxidants (reductants) is detected as electrical signal produced by oxidation of an electrode under standardized conditions without determining contributions of individual molecules involved (Roychoudhury

et al. 2017a, b; Agarwal et al. 2018; Polson et al. 2018). Based on the electrochemical technology, the MiOXSYS system uses a platinum-based electrode sensor with an Ag/AgCl reference cell, and a galvanostat-based analyzer, which completes the circuit. A small volume (~30 μl) of liquefied semen sample is added to the pre-inserted sensor and allowed to flow across the working electrode and to fill the reference cell, thereby completing the electrochemical circuit. Voltage is measured between the reference cell and working electrode every 0.5 s (or 2 Hz), while the counter is set to a voltage sufficient to achieve a 1 nA stabilizing current. The resulting ORP measurement is displayed in millivolts (mV) reflecting a net average of the run (Roychoudhury et al. 2017a, b). The entire process takes less than 5 min. The raw ORP value displayed by the analyzer (mV) is divided by the sperm concentration (sperm count × 10^6/mL) to obtain the normalized ORP, which is expressed as mV/10^6 sperm/mL (Agarwal et al. 2017a).

In the diagnosis of male infertility, the role of ORP as a surrogate marker to conventional semen quality parameters is a current topic of investigation by a number of researchers and clinicians. It facilitates wider application of oxidative stress measurement in clinical and research settings. ORP can be measured in neat semen and seminal plasma and the measurements are not affected by the age of semen or seminal plasma for up to 2 h of liquefaction (Agarwal et al. 2016b). ORP correlates negatively with conventional as well as advanced semen quality parameters, such as sperm concentration (Agarwal et al. 2016b, 2017a; Agarwal and Wang 2017; Roychoudhury et al. 2017a, b; Toor et al. 2016), total sperm count (Agarwal et al. 2016b, 2017a; Toor et al. 2016), total motile sperm count (Al Said et al. 2017), motility (Agarwal et al. 2017a; Agarwal and Wang 2017; Toor et al. 2016), morphology (Roychoudhury et al. 2017a, b; Majzoub et al. 2017), and DNA fragmentation (Arafa et al. 2017) confirming the association of oxidative stress with poor semen quality.

ORP values can differentiate the degree of oxidative stress-induced male factor infertility. Using a cohort of fertile and infertile men from USA a seminal ORP cutoff value 1.36 mV/10^6 sperm/mL was established for distinguishing fertile men from infertile patients (Agarwal et al. 2017a). A couple of studies conducted collectively and individually between Cleveland Clinic (USA) and Doha (Qatar) recommended similar ORP cutoff values 1.41 and 1.42 mV/10^6 sperm/mL to distinguish fertile from infertile men (Agarwal et al. 2017b; Arafa et al. 2018). Recently, from a cohort of fertile and infertile men in India, Roychoudhury et al. (2017a, b) established a seminal ORP cutoff 1.23 mV/10^6 sperm/mL to distinguish healthy men from infertile patients. Furthermore, ORP is highly predictive of oligozoospermia and asthenozoospermia (Agarwal et al. 2017b), and an ORP cutoff 2.59 mV/10^6 sperm/mL best predicted oligozoospermia using a cohort of men from USA (Agarwal and Wang 2017). Monitoring seminal ORP levels over time may help predict the efficacy of antioxidant therapies and define effective doses and durations of treatment. Monitoring ORP as a marker of oxidative stress has also been proposed in cases of leukocytospermia because ORP values paralleled the levels of biomarkers of active inflammation (Hagan et al. 2015; Sikka et al. 2016).

In the human body, the sperm cells live in an aerobic environment like all other cells, and hence, are exposed to different redox states depending on the prevailing

circumstances (Naviaux 2012; Agarwal et al. 2016a, b). ORP can also be measured in cryopreserved semen samples, which is important in predicting the success of assisted reproductive techniques (ART) (Agarwal et al. 2016b). In ART procedures sperm cells are exposed continuously to several culture media and incubating conditions starting from sperm preparation to sperm cryopreservation. An optimum redox potential is required for successful embryogenesis and to avoid teratogenesis (Ufer et al. 2010), and the ORP of the culture medium might be involved in the regulation of the fertilization process (Panner Selvam et al. 2018). It is important to maintain the ORP of culture media on the lower side in order to neutralize and counteract ROS produced especially during the centrifugation process of abnormal semen samples from infertile men (Agarwal et al. 2014b). Determination of ORP values of 10 different culture media commonly used for sperm preparation and ART revealed lower values of the sequential culture medium and one-step culture medium compared to the sperm wash media. SAGE-1-Step medium recorded the lowest ORP value of 208.63 mV (Panner Selvam et al. 2018). In intracytoplasmic sperm injection (ICSI), during sperm processing seminal plasma (that contains protective antioxidants) is removed keeping the sperm cell vulnerable to possible attack by toxic oxygen metabolites generated by immature spermatozoa and leucocytes (Aitken and Baker 1995; Zini et al. 2009). In ICSI procedures, post-washed sperm specimens are loaded into a microdroplet containing a viscous medium of polyvinylpyrrolidone or hyaluronic acid that slowdown the sperm movement thereby facilitating sperm selection, handling and immobilization (Roychoudhury et al. 2018). Comparison of ORP levels of sperm cells exposed to polyvinylpyrrolidone and hyaluronic acid in an experimental ICSI study suggested lower ORP levels in polyvinylpyrrolidone-selected sperm than using hyaluronic acid after 20 min and 1 h of exposure. This indicated that the lower levels of oxidative stress are found in washed sperm cells selected in the polyvinylpyrrolidone-based medium (Roychoudhury et al. 2018). In another clinical study on embryo quality and clinical pregnancy rate, patients with low seminal ORP (<1.36 mV/10^6 sperm/mL) had higher clinical pregnancy rate in comparison to the group with high ORP (Ayaz et al. 2017).

Discrete measures of free radicals, antioxidant activity, and oxidative damage suggest an ambiguous relationship between the redox system and male fertility. Measuring ORP can help rule in male infertility cases associated with oxidative stress that would otherwise go undetected with a conventional semen analysis. Data generated from recent clinical and experimental studies poses ORP as a novel, independent and robust diagnostic marker of male infertility.

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