

Review Article

Oxidative Stress in Assisted Reproductive Technology

Annika Sinha¹ and Sajal Gupta^{2*}¹Case Western Reserve University, USA²Department of Urology, American Center of Reproductive Medicine, USA

*Corresponding author

Sajal Gupta, Department of Urology, American Center of Reproductive Medicine, USA, Email: guptas2@ccf.org

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Abstract

Assisted reproductive technology (ART) has been utilized since 1981 as a therapeutic intervention for both explained and idiopathic infertility. Despite its successes, ART can be associated with complications, such as inability to achieve clinical pregnancy, low birth weight, preterm birth, and other more serious maternal outcomes. However, the etio-pathogenesis of these problems has not been clearly characterized. Both previous and current literature suggests that underlying oxidative stress may be related to adverse ART outcomes. Oxidative stress is an underlying factor in male and female infertility and subsequently has a significant impact on ART success. The presence of reactive oxidative radicals has been linked to poor gamete quality, dysfunctional fertilization, and inability to achieve pregnancy. The production of this oxidative imbalance is not only secondary to pre-existing pathologies, but also is related to aging, genetic predisposition, modifiable risk factors, homeostatic mechanisms, and ART-specific protocols.

This article is a comment on the existing literature regarding the association of oxidative stress in both male and female pathology, the effect of oxidative damage on gamete viability and competence, the intrinsic and extrinsic factors that increase oxidative stress, and possible interventions to neutralize the excessive reactive oxidative stress. Oxidative stress can be reduced in in-vitro conditions by utilization of prudent protocols and in-vivo reduction of oxidative species can be achieved by lifestyle modifications and following a prudent diet. The understanding of both the in-vivo and in-vitro causes of oxidative stress, can then be used to improve reproductive success in both ART and non-ART pregnancies.

INTRODUCTION

By the age of 40, nearly 1 out of 3 couples will face infertility due to both explained and idiopathic causes [1]. Due to this high incidence of infertility, assisted reproductive technology (ART) and related advances in reproductive medicine have addressed both male and female infertility, leading to the first ART-assisted birth in 1981 [2]. The use and popularity of ART has increased dramatically as seen by 160,521 ART procedures completed in 2013 [2].

Despite the numerous successes of ART-assisted pregnancy, clinical pregnancy after ART is achieved in roughly 25% of all IVF cycles [3]. A 2015 retrospective study of 406,334 ART subjects observed the significant differences between demographic and obstetric outcomes of non-ART and ART pregnancies. In this study, significantly more ART pregnancies are complicated by low birth weight and preterm birth [2]. More serious maternal outcomes have been linked to ART, such as abnormal placentation, cardiac morbidity, thromboembolism, postpartum hemorrhage, cesarean delivery, and preeclampsia; however, the incidence of these complications is low [2]. In fact, the most common ART-

mediated effect is twin pregnancies after IVF/ICSI with 40% of all babies after ART born as a twin [4].

Generation of oxidative stress

Evidence of poor outcomes raises questions about causes of these complications and the role of oxidative stress in ART methodology. As aerobic organisms, humans utilize oxygen through mitochondrial and non-mitochondrial pathways in order to produce energy. However, these processes allow for the creation of oxidative stress, which subsequently impairs cellular milieu and functions [5].

Oxidative stress is associated with both male and female infertility. These intrinsic levels of oxidative stress complicate pregnancy outcomes through the presence of elevated reactive oxidative species (ROS) and their adverse effect. Volatile ROS gain stability through electron transfer from biological molecules. Both the DNA of human oocyte and sperm are affected by ROS, causing base oxidation, base de-amination, apurinic/apyrimidic sites of decay, and DNA adducts [6]. This type of damage activates apoptotic pathways, leading to uninhibited programmed cell death [6]. A 2014 mouse study assessed the effects of genetically

induced oxidative stress on both male and female fertility [1]. The group studied the effect of a mutation in an enzyme homologous to succinate dehydrogenase cytochrome b subunit of Complex II [1]. Deficiency in this protein allows for electron leakage, creating damaging ROS. Male mice with induced mitochondrial deletions were observed to suffer from male infertility, abnormal spermatogenesis, and elevated superoxide anion concentrations [1]. Similarly, female mice also had increased superoxide anion levels and ovarian dysfunction due to reduced mitochondrial electron transport [1].

In the perspective of fertilization and embryo development, the protection against ROS is vital. While the oocyte has the potential to repair damaged DNA, Yves *et al.* explain that the DNA restoration pathways of the oocyte may not completely correct ROS-mediated sperm damage [6]. Therefore, a mechanism to improve *in vivo* ROS status of both egg and sperm before ART is required to enhance reproductive success [6].

Oxidative stress: associated pathology

Oxidative stress and female pathology: The leading causes of infertility in most reproductive-age females include endometriosis and polycystic ovarian syndrome (PCOS). Even though the human body naturally produces ROS as a byproduct of cellular metabolism, both conditions are associated with high levels of oxidative stress and damage, which can significantly hinder fertility [7]. Endometriosis is a benign disease characterized by the presence of extra-uterine endometrial lesions [7]. This disease affects more than 10% of all women of reproductive age. In recent studies, endometriosis patients displayed significantly higher levels of ROS markers, such as ceruloplasmin and 8-hydroxy-2-deoxyguanosine [8,9]. Moreover, these patients also maintained decreased total antioxidant status and lower thiol levels, which are correlated with severity of endometriosis [8,10]. In endometriosis patients, Preito *et al.*, found that those with endometriosis-related infertility had lower vitamin C levels than women with other types of infertility [11]. This finding reiterates the imbalance between physiological oxidants and antioxidants in the disease condition [11].

This abnormal oxidative balance is suggested to cause low pregnancy rates in women with endometriosis. While not completely understood, endometriosis reduces oocyte quality. Pellicer *et al.* studied the origin of this subfertility by comparing pregnancy and implantation rates in women with either endometriosis or tubal infertility. There was a significant decrease in pregnancy rate and implantation rate in women with endometriosis than in women with tubal infertility [12]. Moreover after 72 hours, the embryos of endometriosis patients were of poor quality as demonstrated by low blastomeric number, which is suggestive of abnormalities in fertility [12]. Therefore, it appears that endometriosis-mediated combination of decreased antioxidant concentrations, increased ROS, and dysfunctional oocytes can fail to facilitate viable pregnancies [13].

As another cause of female infertility and chronic hyperandrogenic anovulation, PCOS is also associated with high levels of oxidative stress [14]. The etiology of PCOS is thought to be based on insulin resistance, causing obesity, central adiposity, and hypertension in patients. This insulin resistance mediates

an rise in androgen production in the adrenals and ovary [13]. The resulting hyperglycemia increases pro-inflammatory TNF- α levels [13]. TNF- α causes subsequent oxidative stress, negatively affecting mitochondrial function and oxidative balance. [13]. The pathogenesis of this oxidative stress appears to be based on decreased mitochondrial oxygen consumption, low antioxidant levels, and, most importantly, increased ROS production from inflammatory mononuclear cells [13].

A systematic review of 1633 potential studies on the relationship between oxidative stress markers and PCOS was conducted [14]. In contrast to control group of women, women with PCOS were found to have a 23% increase in homocysteine, a 47% increase in malondialdehyde, a 36% increase in asymmetric dimethylarginine, a 34% increase in superoxide dismutase activity, and a 50% decrease in glutathione levels [14]. These results coupled with the strict inclusion criteria and clinical parameters for this PCOS review further reiterate the role of oxidative stress in PCOS. PCOS also causes increased LH secretion, excess androgen production, abnormal hypothalamic-pituitary-ovarian axis, follicular atresia, menstrual irregularity, and infertility [15]. Based on these abnormalities, PCOS is linked to decreased female fecundity. In a 2014 prospective population-based cohort study, teenage girls with menstrual irregularity secondary to PCOS were observed to be at a higher risk of infertility problems at age 26 [16]. Based upon the review of studies and meta-analysis, there is underlying oxidative stress in PCOS patients.

Oxidative stress and male infertility: While large scale neutralization of ROS through vitamin supplementation seems troublesome, male infertility associated with increased ROS is the cause of infertility in 20% of all infertile couples. Much of this oxidative stress detrimentally affects sperm functioning, including motility, sperm count, and capability to achieve fertilization [1].

The increased levels of ROS in male infertility are directly correlated with sperm morphology, one of the markers of sperm function. Currently, both sperm count and motility are primarily used for sperm evaluation; however, according to a 2014 study, sperm morphology may also be valuable predictor of pregnancy success [21]. The morphology of sperm is the product of multiple cellular modifications that can indicate abnormal structural defects and changes, giving researchers clues about the mechanism related to sperm health. Immature or defective sperm produce high levels of ROS, further cementing the correlation between ROS and infertility. Analysis of the correlation between seminal oxidative stress and male infertility was conducted in 79 patients with teratozoospermia and 56 healthy subjects [21]. Moreover, patients with teratozoospermia had significantly higher levels of ROS compared to controls [21]. This study demonstrated high ROS levels and poor sperm morphology were related in patients with male infertility [21].

In addition to changes in sperm morphology, ROS mediate changes in seminal fluid leukocyte concentrations, which have been postulated to affect fertility. Relative leukocyte concentrations and ROS production were studied in 14 control subjects and 21 sub-fertile patients [22]. Greater numbers of leukocyte/ 10^6 spermatozoa were associated with detectable ROS

in both groups [22]. Despite this association, the relationship between concentration of leukocytes and sperm concentration is debated, given that lower sperm counts directly affect fertility [23]. Using a prospective clinical design with 56 infertile patients and 13 controls, Aziz *et al.* found that leukocyte concentrations were negatively correlated with poor functioning sperm, but did not correlate with sperm concentration [23]. Regardless of this controversy, there is an established link between leukocytospermia and infertility because of leukocyte-mediated production of oxidative stress [23].

In almost 50% of infertile men, the cause of infertility is relatively unknown; however, the literature suggests a genetic basis for the condition. In males, both the Y and X chromosome have roles in infertility. In 2013 study, a mutation in an infertility associated gene on the X chromosome (USP26) was reported to be associated with azoospermia and recurrent pregnancy loss [24]. USP26 functions as an ubiquitin-specific protease that removes histones during protamination; however, mutations in this gene cause increased DNA damage, decreasing the integrity and function of the sperm. In this study, the DNA of 166 infertile Iranian men with non-obstructive azoospermia were compared to that of 60 fertile subjects [24]. Three different types of USP26 mutations were noted, and expression levels for USP26 significantly differed between the control and experimental groups [24]. Moreover, Paduch *et al.* reported no live deliveries in couples with mutations in USP26 [24]. While Asadpor *et al.* described a genetic basis for male fertility, the study itself was limited to the Iranian population and haplotypes with the 3 mutations were also seen in the unaffected control group [24]. No conclusive reasoning was given for the mutations in the control group, but this literature does show that genetic predisposition may also intrinsically affect sperm DNA.

Along with USP26 mutations, high levels of sperm DNA fragmentation are associated with poor-quality semen and failed fertilization. Simon *et al.* assessed sperm DNA fragmentation in both native sperm and sperm samples after density-gradient centrifugation in 203 couples completing IVF and 136 completing intracytoplasmic sperm injection (ICSI) [25]. In practice, couples with less than 50% of DNA fragmentation utilize IVF while those with more than 50% DNA fragmentation use ICSI. IVF utilizes natural selection via *in vivo* fertilization while ICSI bypasses natural selection by allowing the clinician to select for the most visually viable sperm for fertilization. In this study, patients were categorized by their ability to undergo either IVF or ICSI in hopes of achieving successful clinical pregnancy [25]. In the IVF group, couples with less than 25% sperm DNA fragmentation had a live birth rate of 1 in 3; whereas, couples with more than 50% sperm DNA fragmentation had a 13% live birth rate [25]. In conclusion, this study suggested that sperm DNA damage is inversely proportional to live birth rates in couples undergoing IVF.

Understanding oxidative stress risk factors

Optimization of ART protocols: Along with physiological creation of ROS, ART protocols, such as sperm preparation, can directly alter the amount of oxidative stress present in these cells. Both sperm sample preparation and culture conditions can adversely affect IVF success. In order for successful IVF, ejaculate must be properly prepared to remove seminal liquid,

epithelial cells, necrotic sperm, and other blood cells. These extra components can produce toxic, reactive substances, which can reduce fertilization rates. The most common methods of sperm preparation include density-gradient centrifugation. This process includes spinning the sperm sample to allow viable sperm to a sperm pellet. However, increased duration of centrifugation of sperm can significantly increase the levels of oxidative species [26].

The impact of oxygen on the embryo culture also affects outcomes. The amount of oxygen in contact with embryos directly influences the amount of oxidative stress in the system. According to Gardner *et al.* most embryos in IVF laboratories experience significant oxidative stress due to oxygenation [27]. In this analysis of oxygenation protocols of numerous IVF labs, Gardner *et al.* determined that the most common factor among cases with adverse outcomes was the use of atmospheric oxygen (~21%) for embryo culture [27]. However, clinics using physiological concentrations of oxygen (~5%) reported no adverse outcomes [27]. The conclusion of this review called for revisions to protocols using 20% oxygen in IVF cultures – a practice that still occurs worldwide [27]. By lowering the oxygen content, embryos will suffer less molecular and cellular damage, leading to more successful IVF [27].

Interventions to Ameliorate Oxidative Stress: To improve reproductive outcomes in infertile patients, the use of antioxidant supplementation to improve outcomes has been considered. Infertile patients may have intrinsically high levels of oxidative stress, disrupting oxidative balance. As previously described, endometriosis is associated with increased oxidative stress and low antioxidant status. In endometriosis patients, eight weeks of vitamin C and E antioxidant supplementation not only reduced concentrations of inflammatory markers, but also reduced inflammation-mediated pain by 43% [17]. This finding supports the theory that dietary antioxidant consumption can be inversely proportional to oxidative stress and its effects, inflammation and pain, even in patients with intrinsically high oxidative status.

Contrastingly, a 2015 RCT suggests that supplementation does not confer any reproductive improvement in women undergoing IVF [18]. This RCT separated women undergoing IVF/ICSI into 2 groups: control group (n=106) and an experimental group (n=112) that received daily oral antioxidants [18]. Women in the experimental group received a combination antioxidant cap, including vitamin A 3000 IU, vitamin C 90 mg, vitamin E 15 IU, at the onset of counseling [18]. The researchers used the number of mature metaphase (MII) oocytes and clinical pregnancy rate as the process outcomes [18]. It was found that there was no statistically significant difference between the control and experimental patients [18]. While this is one of the largest RCT studies to date, this study also was limited by the un-blinding of the physician, lack of data on live birth rates, and the short 2.5 month duration of the study [18]. Despite these limitations, this study does assess more than one outcome. Because both clinical pregnancy and mature metaphase oocyte counts are used, one can have a better understanding of the cellular effects of ROS and the broader outcome of clinical pregnancy.

Moreover, specific antioxidant species, such as vitamin A, vitamin E, and vitamin C, have also not been associated with

reduction of oxidative biomarkers in other studies [19]. While investigating the effects of these three vitamins on ROS, Kazemi *et al.* were unable to find any significant associations between vitamins E and A intake levels and follicular fluid ROS markers in an observational prospective study of 219 IVF/ICSI patients [19]. However, vitamin A intake was related to normal embryonic cleavage rate [19]. Interestingly, vitamin C was linked with normal fertilization rate, MII stage oocyte rate, and percentage of cleaved embryos [19]. While the antioxidants did not seem to lower ROS, they did confer better reproductive outcomes, suggesting some benefit to antioxidant supplementation.

While some reports consider antioxidant supplementation as beneficial, other studies are adamantly against this process due to the lack of effectiveness and potential negative side-effects [20]. In a significant review of the “antioxidant myth,” Gutteridge *et al.* challenges the idea that antioxidant supplementation is favorable for populations with normal diet and lifestyles [20]. This article suggests the over-consumption of exogenous antioxidants lower endogenous antioxidant levels [20]. Additionally, the theory of the “antioxidant paradox” in male infertility further adds to the idea that supplementation may not be beneficial. The antioxidant paradox is based on the idea that a certain level of ROS is essential for homeostasis, such as in acrosome reactions [21]. With increased antioxidant levels via supplementation, the body might be susceptible to cellular dysregulation, such as cancer [21].

Despite the clear debate in the benefits of supplementation, many literature reports relate low oxidative status and subsequently less ROS-associated cellular damage to improved reproductive outcomes [22]. While the mechanism to stabilize ROS levels has yet to be elucidated, the beneficial effects of oxidative balance on pregnancy are well established. In recent 2013 study of 102 women undergoing ICSI and embryo transfer, higher levels of serum total antioxidant response (TAR) indicated improved ability to achieve clinical pregnancy due to low oxidative stress [22]. Studies, similar to that of Velthut *et al.* validate the dangers that uncontrolled ROS accumulation can have on ART success [22].

Lifestyle Modifications – Interventions to Reduce in Intrinsic Oxidative Stress: Lifestyle factors, both modifiable and non-modifiable, have drastic impacts on infertility and pregnancy success. Exposures to polychlorinated biphenyls (PCB), organophosphorus, lead, and bisphenol A can adversely affect fertility. In a 2005 cross-sectional study of 707 men assessed the impact of dietary PCB and other organochlorine pollutants on sperm chromatin integrity [23]. These pollutants bioaccumulate in predatory fish; therefore, men of both European and Inuit lineages from Greenland, Sweden, Poland, and Ukraine with fish-based diets were recruited [23]. In this study, both sperm chromatin structure assays and levels of CB-153, a proxy for total PCB levels, were used as outcome measures [23]. The results showed strong increasing levels of DNA fragmentation with increasing levels of CB-153 in European men; however, the same relationship was not found in Inuit men [23]. This study suggests dietary PCB may have some impact on chromatin structure; however, other background and lifestyle factors may also determine the extent of DNA damage.

Moreover, environmental factors, such as Wifi- and cellular

phone-induced electromagnetic radiation and heat stress due to summer and body temperature, have also been assessed as risk factors for increased ROS [24]. In this review, evidence of Wifi-mediated damage was noted by Oksay *et al.* and Avendaño *et al.* [24,26]. Oksay *et al.* observed that Wifi (60 min/day for 30 days) caused ROS damage in the testis [25]. Similarly, Avendaño *et al.* noted that Wifi caused an increase in DNA fragmentation and a decrease in sperm motility [26]. Because many of these everyday exposures can impact fertility, counseling about such risk factors is advised [27].

Other pertinent modifiable risk factors include smoking and obesity. In a 2014 analysis of maternal smoking habits on ROS production, Ardalic *et al.* found that smokers during pregnancy had increased levels of modified peroxidative products, evidence of ROS-mediated changes [28]. Active smoking also had negative effects on IVF outcomes and ovarian reserve. In a 2008 study, Freour *et al.* found that the 40 women who were smoking during their IVF cycles had decreased ovarian response to hyperstimulation and a low rate of clinical pregnancy in comparison to the control patients [29]. According to a 1980 study, smoking itself was associated with risk of spontaneous abortion, especially in conjunction with alcohol use [30]. However, for heavy and moderate smokers, quitting is often difficult to achieve. Regardless of this problem, reducing the number of cigarettes and nicotine exposure can offer some reproductive improvement. In a large study of data from 47,000 babies born over 5 years, light smoking (<10 cigarettes a day) affected birth and placental weight; however, stillbirth rates, abortion rates, and postnatal outcomes on the 28th day of life were similar to those in the non-smoking group [31]. This study can offer some practical advice to clinicians and patients to reduce nicotine loads – even if quitting is not possible.

Like smoking, obesity is related to both male and female subfertility. In men specifically, obesity can lead to altered semen parameters, such as abnormal morphology, motility, chromatin, and concentration. These deficits in sperm can manifest as erectile dysfunction, a common cause of infertility. According to Corona *et al.* approximately 96% of men with metabolic syndrome displayed erectile dysfunction [32]. Mouse studies of diet-induced obesity suggest that maternal obesity causes mitochondrial changes in oocytes, such as abnormal homeostasis, spindle formation, and distributional pattern. These changes are thought to lead to female infertility due to poor oocyte quality [33]. Therefore, changes in modifiable risk factors, such as avoiding smoking and heat, losing weight, and eating a diet rich in antioxidants can be used as treatment for oxidative stress [27].

The role of non-modifiable patient risk factors: Finally, non-modifiable factors, such as age and genetic predisposition, also have significant impacts on infertility. Both advanced maternal age (greater than 40 years of age) and advanced paternal age can cause delay conception and result in nonviable pregnancy or early pregnancy loss. In non-ART assisted pregnancies, women of advanced maternal age were linked to increased miscarriage and pre-eclampsia risks in a retrospective cohort study [34]. In the Katib *et al.* discussion of reproductive aging, aging itself probably increased oxidative stress as cellular function diminishes over time, leading to increased use of IVF

with suboptimal success rates [35]. A retrospective study of 6022 semen samples assessed multiple semen parameters: volume, motility, quality and their relationship to sperm function [36]. In this study, good sperm parameters (volume, motility, quality, and function) were seen in patients between 30-35 years of age with a significant decrease in quality after age 55 [36]. This significant reduction in sperm parameters was inversely proportional to increasing aging, suggesting the pronounced effects of male aging on reproductive outcomes. This study is not only one of the largest on the effects of male aging, but also the data was handled by the same biologist, which enhanced the study design due to lack of bias. Higher percentage of couples in advanced age is seeking the ART option. This study concluded that advanced age couples have significantly lower reproductive success with ART.

CONCLUSION

The impact of oxidative stress is seen both male and female fertility and in turn has an impact on IVF success. Because a dependence on aerobic respiration, humans produce reactive molecules, which mediate adverse cellular changes [1]. These changes include ROS generation, lipid peroxidation, mitochondrial injury, and DNA damage [6]. Both these factors limit the effectiveness and integrity of gametes to achieve healthy and successful pregnancies. Reproductive aging has led to the use of IVF, which is increasingly being considered as a solution. However, even IVF can be detrimentally affected by ROS generated through intrinsic and extrinsic factors, cellular processes, genetic predisposition, modifiable risk factors, age-related consequences, and IVF protocols. While cellular processing, genetic predisposition, and age are all non-modifiable, awareness about the effects of modifiable determinants, such as diet, occupational exposure, and smoking, can improve patient awareness and outcomes. Additionally, remedies, such as antioxidant supplementation, can reduce *in vivo* ROS production while IVF protocol adjustment and modifying *in vitro* conditions can address *in vitro* issues. Addressing ROS production with optimal antioxidant interventions, lifestyle changes, and reduction of ROS generation in ART conditions maybe the way forward to enhance reproductive success rates, both for natural and assisted fertility.

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