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Oxidative stress in an assisted reproductive techniques setting

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Objective: The manipulation of gametes and embryos in an in vitro environment when performing assisted reproductive techniques (ART) carries the risk of exposure of these cells to supraphysiological levels of reactive oxygen species (ROS). The main objective of this review is to provide ART personnel with all the necessary information regarding the development of oxidative stress in an ART setting, as well as the sources of ROS and the mechanisms of oxidative stress-induced damage during ART procedures. The impact of oxidative stress on ART outcome and the different strategies designed to prevent it are also discussed.

Design: Review of international scientific literature. A question-and-answer format was adopted in an attempt to convey comprehensive information in a simple yet focused manner.

Result(s): The pO₂ to which gametes and the embryo are normally exposed in vivo is significantly lower than in vitro. This results in increased production of ROS. Increase in levels of ROS without a concomitant rise in antioxidant defenses leads to oxidative stress. Lipid, protein, and DNA damage have all been associated with oxidative stress. This may ultimately result in suboptimal ART success rates.

Conclusion(s): Many modifiable conditions exist in an ART setting that may aid in reducing the toxic effects of ROS. (Fertil Steril® 2006;86:503–12. ©2006 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction, embryo, oocyte oxidative stress, reactive oxygen species

The presence of oxidant and antioxidant systems in various reproductive tissues has evoked great interest on the role of oxidative stress in human reproduction. Oxidative stress has been defined as an elevation in the steady-state levels of various reactive oxygen species (ROS) that exceeds the body's antioxidant defenses (1). This has been implicated in a number of different reproductive scenarios such as endometriosis, folliculogenesis, oocyte maturation, hydrosalpingal fluid, necrozoospermia, asthenozoospermia, and sperm DNA damage. Oxidative stress can also be involved in the etiology of defective embryo development (2, 3). Furthermore, oxidative stress may play a role after embryo transfer. The posttransfer-preimplantation time could be detrimental to the implantation process itself. The presence of the transferred embryos in a microdrop of culture media hanging in

the endometrial cavity before the initiation of implantation could expose those embryos to the various components of the endometrial environment.

Assisted reproductive techniques (ARTs) have become the treatment of choice in many cases of male and female infertility. Despite numerous advances, the current success rates of these procedures remain unsatisfactory (4, 5). Knowledge of the factors that impact ART outcome may help increase success rates and, in turn, alleviate the socioeconomic burden imposed on patients and on public and private health institutions. Among the various factors that negatively affect ART outcome, oxidative stress has recently emerged as one of the most important ones (1, 6–8).

It is generally accepted that an in vitro setup can never mimic the exact physiological conditions of an in vivo system. Multiple factors impinge on an IVF setting leading to an increase in oxidative stress and suboptimal ART outcome. This review summarizes the latest evidence on the evolution of oxidative stress in an ART setting and should help identify those factors that contribute to oxidative stress

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in the ART laboratory. The necessary information on how to minimize and prevent oxidative stress is also provided.

DEVELOPMENT OF OXIDATIVE STRESS IN AN ART SETTING

How Does Oxidative Stress Generally Develop?

Reactive oxygen species are oxygen-derived molecules that act as powerful oxidants. Reactive oxygen species, such as superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($OH^{\cdot}$), are formed as intermediary products in low concentrations in the male and female genital tracts (6). Reactive oxygen species have the ability to react with any molecule and modify it oxidatively, resulting in structural and functional alterations (9). Reactive oxygen species are neutralized by an elaborate defense system consisting of enzymes such as catalase, superoxide dismutase, and glutathione peroxidase or reductase, and numerous non-enzymatic antioxidants such as vitamin C, vitamin E, vitamin A, pyruvate, glutathione, taurine, and hypotaurine (10). Under physiological conditions, ROS and antioxidants maintain a stable ratio. A shift toward ROS will give rise to oxidative stress.

Why Should We Expect the Development of Oxidative Stress during IVF?

The effects of oxidative stress in an ART setting may be amplified due to the lack of physiological defense mechanisms available and due to the number of potential sources of ROS at play. Oxidative stress has been implicated in the etiology of infertility. The role of oxidative stress in the pathogenesis of male factor infertility has been documented in numerous studies (10, 11). Sperm damage induced by oxidative stress includes membrane and DNA damage leading to necrozoospermia, asthenozoospermia, and DNA fragmentation. Use in ART of spermatozoa that have been damaged during maturation in the seminiferous tubules epithelium, sperm transport through the epididymis, or during sperm processing in the ART lab may result in altered oocyte and/or embryo development. In the context of female infertility, oxidative stress has been poorly characterized (6). Nevertheless, oxidative stress indices in the female reproductive system have been demonstrated to correlate with fertility. Certain ROS levels and selenium-dependent glutathione peroxidase activity in follicular fluid have been positively correlated with pregnancy rates (PRs) (12, 13). Other markers of oxidative stress in follicular fluid such as lipid peroxidation, total antioxidant capacity, and superoxide dismutase activity are also strongly correlated with oocyte fertilization and pregnancy rates following IVF (7, 14, 15). In addition, 8-hydroxy-2'-deoxyguanosine—an important oxidative stress marker in granulosa cells—displays a negative correlation with embryo quality following IVF (16).

Can Human Gametes Counteract Oxidative Stress?

Human gametes possess natural antioxidant defenses. A decrease in their total antioxidant capacity (TAC) may lead

to oxidative stress. The environment surrounding the oocyte and embryo contains nonenzymatic antioxidants such as vitamin C, glutathione, hypotaurine, and taurine, which protect the embryo from external sources of ROS (17). The levels of these antioxidants may be indicative of the extent of oxidative stress. Although TAC levels do not differ in the follicular fluid whether the follicle contains an oocyte or not, they are significantly higher in fluid from follicles where the oocyte successfully fertilizes (14). However, TAC levels were also reported to be significantly lower in the follicular fluid from follicles where the resulting embryo survived until transfer (14), which indicates that the role of TAC in folliculogenesis and early embryonic development remains controversial.

On the other hand, spermatozoa have limited antioxidant defenses because their cytoplasm contains low concentrations of scavenging enzymes. Moreover, they are particularly susceptible to oxidative stress-induced damage due to the high content of polyunsaturated fatty acids in their membranes (18). Nevertheless, the sperm midpiece contains superoxide dismutase and glutathione peroxidase as well as α -glutamyl transpeptidase, which regulates the glutathione content of the oocyte, thus providing protection against oxidative stress (19).

In the male reproductive tract, somatic and germ cells are maintained within a delicate balance of oxidants and antioxidants. Minimal levels of oxidants are needed for the physiological regulation of processes such as capacitation and acrosome reaction (20); however, if these levels increase above a critical threshold, they result in structural and functional damage, which may lead to motility loss, premature acrosomal reaction, lipid peroxidation, apoptosis, and DNA damage (21–25). Antioxidants can protect against some of these events (26–28).

REACTIVE OXYGEN SPECIES PRODUCTION IN AN ART SETTING

How Are ROS Produced during ART?

Reactive oxygen species can be produced either intracellularly, originating from gametes, or extracellularly from environmental factors. A potential source of ROS in the ART media is its generation during the preparation of semen due to the activation of ROS production by immature spermatozoa by centrifugation, the absence of the antioxidant-rich seminal plasma, or contamination by leukocytes. Moreover, spermatozoa selected for ART most likely originate from an environment experiencing oxidative stress, and a large percentage of these sperm may already have DNA damage before semen processing (29). Similarly, oocytes and embryos contribute to the increase in ROS levels because of their metabolism and the lack of the protective antioxidant mechanisms present in their natural habitat (2, 30). The external environment that surrounds the ART procedure also plays an important role in the development of oxidative stress. The most important external factor that may affect

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