

Oxidative Stress and Female Infertility

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The etiology of unexplained infertility and recurrent pregnancy loss remains unclear and poses a challenge to clinicians involved in infertility diagnosis and treatment. Recent and ongoing studies in our laboratory suggest that oxidative stress may be a potentially treatable pathological factor affecting female fertility.

Oxidative stress (OS) results when the level of reactive oxygen species (ROS) exceeds the capacity of antioxidants to neutralize them. In females, OS is hypothesized to negatively impact a number of processes involved in reproduction, including folliculogenesis, oocyte maturation, endometriosis and embryo development. OS may damage the cellular membrane, retard embryo development and induce cellular apoptosis.

The cause and effect relationship between OS and female infertility has yet to be established. However, the demonstrated association between the two suggests that controlling ROS production during assisted reproduction techniques (ART) may improve success rates for implantation and pregnancy.

During ART, ROS may originate from multiple oocytes in a dish, large cumulus cell mass, or the spermatozoa used for insemination and embryos. The presence of metallic cations, light exposure and oxygen concentration are all factors in the culture media that can increase embryo production of ROS.

ROS also may be present in follicular fluid or in semen. In a meta-analysis by our group, ROS levels in semen were shown to adversely affect the fertilization rate with IVF. Based on these findings, measuring ROS levels in ART culture, embryos, follicular fluid or semen may be useful in counseling patients regarding failed IVF/ICSI and in planning future attempts.

For maximum effectiveness, ROS and OS levels should be evaluated at the point when an infertile woman is first considering ART. ROS level may be measured by flow cytometry and chemiluminescence, and total antioxidant capacity in

the follicular fluid or embryo culture media. ROS in culture media may impact post-fertilization development, i.e. cleavage rate, blastocyst yield, and embryo quality (indicators of ART outcome).

In the event these evaluations demonstrate high levels of ROS and OS, a multi-pronged approach is recommended to address these issues during ART.

Managing culture media conditions to reduce OS is a first-line consideration. This can be accomplished by supplementing the culture media with antioxidants and metal chelators such as vitamins C and E, thiol, antioxidant enzymes and hypotaurine.

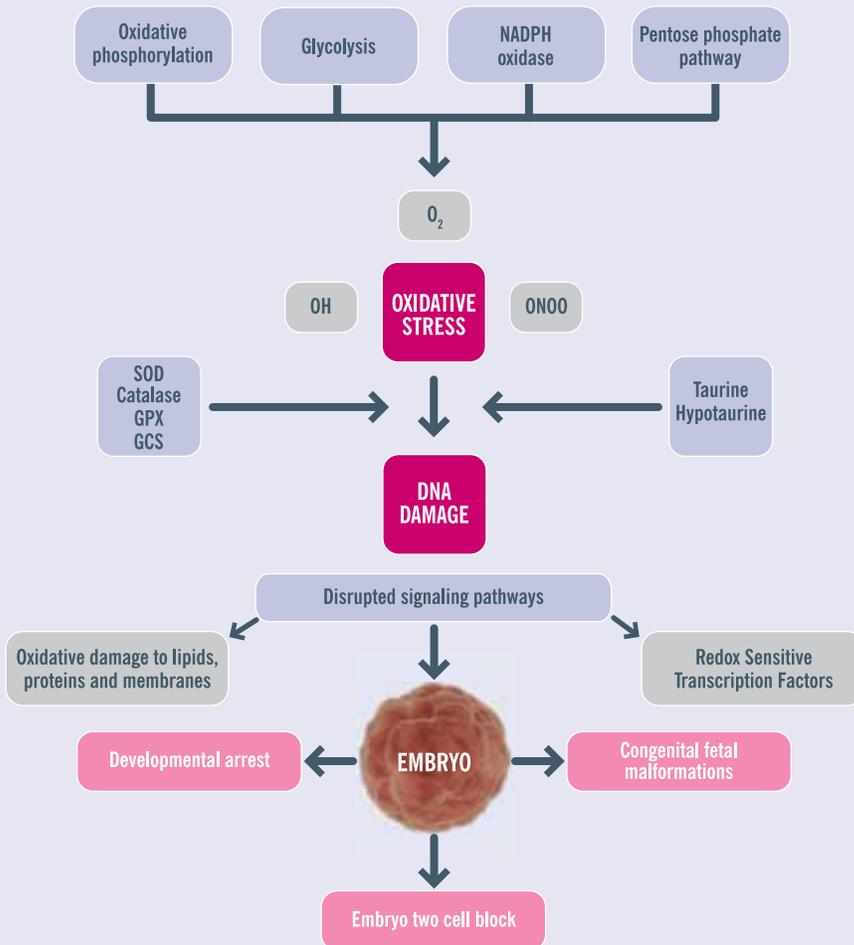
Reducing seminal OS is important for both natural and assisted fertility. Selecting an optimal semen preparation technique is the next step for preventing or controlling OS. The swim-up or one-step wash techniques have been shown to minimize ROS production.

As a final recommendation, antioxidant supplementation should be considered in infertile women with high OS and ROS levels. There is a potential role for well-balanced nutrition and medicinal herbs to achieve adequate levels of antioxidants in vivo, and the prevention and treatment of reproductive diseases such as preeclampsia and ovulatory disorder infertility.

Our knowledge of OS and its effects on fertility and ART outcomes is evolving rapidly. Our laboratory will continue to be on the leading edge with studies to evaluate the presence of ROS in commercially available ART culture media and the



Oxidative stress in the ART setting



use of antioxidant supplementation in female infertility with the goal of achieving higher live birth rates via natural conception and in ART. ⁿ

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