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Impact of oxidative stress on female fertility

Elizabeth H. Ruder[a], **Terryl J. Hartman**[b], and **Marlene B. Goldman**[c]

[a] Cancer Prevention Fellowship Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland [b] Department of Nutritional Sciences, Pennsylvania State University, University Park, Pennsylvania [c] Department of Obstetrics & Gynecology and Community & Family Medicine, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA

Abstract

Purpose of review—To review the role of oxidative stress in the context of female fertility.

Recent findings—Oxidative stress is associated with decreased female fertility in animal and in-vitro models, but no studies to date have directly assessed the relationship in women. Exposures associated with oxidative stress and with evidence to influence the timing and maintenance of a viable pregnancy include pregnancy complications (e.g. preeclampsia), extremes of body weight, alcohol, tobacco, and caffeine intake. Intake of antioxidant nutrients, including use of multivitamins, impacts the generation of reactive oxygen species and may play a beneficial role in female fertility.

Summary—Infertility is a significant public health problem and diagnosis and treatment are stressful, invasive, and costly. The role of oxidative stress in female fertility is an understudied and compelling area for investigation. Identifying modifiable factors to decrease oxidative stress in the gynecologic environment may be an inexpensive and noninvasive therapy for increasing fertility.

Keywords

antioxidants; female infertility; oxidative stress

Introduction

Oxidative stress occurs when the generation of reactive oxygen species (ROS) and other radical species exceeds the scavenging capacity by antioxidants due to excessive production of ROS and/or inadequate intake or increased utilization of antioxidants. Most ROS are formed as a consequence of the mitochondrial respiratory chain, but can also be formed by exogenous exposures such as alcohol, tobacco smoke, and environmental pollutants. Antioxidants (including vitamins C and E) and antioxidant cofactors (such as selenium, zinc, and copper) are capable of disposing, scavenging, or suppressing the formation of ROS. Evidence exists supporting the role of oxidative stress in male subfertility, including decreased sperm motility, sperm number, and sperm–oocyte fusion [1]. In women, several animal and in-vitro studies suggest that oxidative stress may affect female fertility but the relationship has not been directly addressed in women trying to conceive. The purpose of this review is to summarize the recent literature linking female oxidative stress, including the influence of dietary anti-oxidants on the timing and maintenance of a viable pregnancy.

Correspondence to Elizabeth H. Ruder, Cancer Prevention Fellowship Program, National Cancer Institute, National Institutes of Health, 6120 Executive Boulevard, Room 150E, MSC 7105, Bethesda, MD 20892, USA, Tel: +1 301 443 5637; eruder@jhsph.edu.

Antioxidant status and vitamin supplementation

Antioxidant nutrients impact ROS in animal models and in humans. Adequate intake of vitamin E protects rats from free radical generation [2] and rats receiving vitamin E supplementation exhibit decreased levels of urinary peroxidation products [3]. In adult women, consumption of antioxidant-rich fruit and vegetables is negatively associated with oxidative stress [4]. Furthermore, anti-oxidants have an important role in the female reproductive system [5]. Recent interest has developed in the joint roles of ROS and superoxide dismutase (SOD), which catalyzes the destruction of the O^{2-} free radical, as second messengers to regulate endometrial function [6]. It was previously known that SOD increased in human endometrial stromal cells with decidualization and was a likely important component of implantation [7]. Antioxidant capacity of follicular fluid during oocyte retrieval has also been associated with characteristics of IVF success. This includes an overall negative correlation between follicular fluid ROS and embryo quality and a favorable effect of ROS on percentage of embryo formation up to thermochemiluminescence of 100 cps in grade II and grade III oocytes and declining embryo formation at higher levels [8]. This work provides support for previous research that an acceptable threshold level of oxidative stress may represent healthy, metabolically active cells [9]. Melatonin, which plays a role in reproduction of seasonal breeding animals, also undergoes seasonal variation in the human preovulatory follicle [10]. Melatonin and its metabolites are direct free radical scavengers and modulate gene transcription for antioxidant enzymes [11–14]. A recent investigation between oxidative stress and poor oocyte quality among women undergoing IVF and embryo transfer indicated that concentration of 8-OHdG (a measure of DNA oxidation) was significantly greater in the follicular fluid with a high rate (≥30%) of degenerative oocytes [15•]. A subset of women who failed to become pregnant in the previous IVF-embryo transfer cycle were provided with 3 mg of melatonin per day, 600 mg α-tocopherol (vitamin E) per day, or both melatonin and α-tocopherol from the fifth day of the previous menstrual cycle to day of oocyte retrieval. Compared with the previous IVF cycle, administration of any of the three treatments was associated with a significantly reduced intrafollicular concentration of 8-OHdG ($P < 0.05$). Hexanoyl–lysine adduct (a measure of lipid peroxidation) was significantly reduced with treatment with α-tocopherol and α-tocopherol + melatonin treatment, but not melatonin alone. In sum, these results suggest that oxidative stress negatively impacts oocyte maturation and supplementation with melatonin or α-tocopherol may protect oocytes from oxidative stress.

Multivitamins are available in a number of formulations, most of which provide at least 100% of the US Recommended Daily Allowances (RDAs) for antioxidant nutrients. A randomized, double blind, controlled trial providing preconception multivitamins to female partners of couples trying to conceive indicated higher rates of conception among the women receiving multivitamins, possibly due to an increase in menstrual cycle regularity [16]. Recent evidence from the Nurses' Health Study cohort indicates a decreased risk of ovulatory disorders among women consuming multivitamins compared with women not taking multivitamins [relative risk (RR) = 0.69, 95% confidence interval (CI) 0.51–0.95; RR = 0.59, 95% CI 0.46–0.75 for women consuming 3–5 tablets and ≥6 tablets per week, respectively, compared with nonconsumers] [17•].

Pregnancy complications

Several studies have examined the role of oxidative stress and pregnancy complications. Two retrospective studies [18,19] reported that reduced antioxidant status increased risk of spontaneous abortion. Vural *et al.* [19] demonstrated that plasma levels of ascorbic acid (vitamin C) and α-tocopherol (vitamin E) were significantly lower in women with recurrent spontaneous abortion, although a prospective investigation is needed to rule out the possibility that lower levels of plasma antioxidants are not a result of the spontaneous abortion rather than

the reverse. ROS have been implicated in the development of premature rupture of the fetal membranes [20,21] and evidence suggests that oxidative stress may be associated with preeclampsia [22,23]. A complexity of these investigations is that pregnancy itself is a source of oxidative stress and little data are available on oxidative stress in the preconception and early conception period. A recent investigation measured urinary isoprostanes (a measure of oxidative damage to lipids) and 8-OHdG among approximately 500 women at less than 16 weeks of gestation with eventual live births [24•]. After adjusting for potential confounders, mean birth weight decreased with increasing 8-OHdG. No relationship of isoprostanes with birth weight was observed, but increasing isoprostane levels were associated with risk of preeclampsia and suggestive of increased risk of preterm delivery. Another recent investigation reported that plasma concentrations of TBARS (thiobarbituric acid reactive substances, a product of lipid peroxidation), protein carbonyls (a product of protein oxidation), and tumor necrosis factor-α (TNF-α) and IL-6 (measures of inflammation) were higher in preeclamptic women less than 20 weeks of gestation compared with controls [25•]. Among preeclamptic individuals, IL-6 and protein carbonyls were highly correlated, suggesting that oxidative stress may enhance the inflammatory response and in turn generate more oxidative stress. Results from the VIP (Vitamins in Preeclampsia) Trial, a randomized clinical control trial providing either 1000 mg vitamin C and 400 IU vitamin E or placebo from 14 to 22 weeks of gestation indicated that high-dose supplementation did not prevent the development of preeclampsia among women at higher risk for developing the condition. Furthermore, supplementation was associated with increased low birth weight [26], thus raising concerns about possible nonantioxidant pleiotropic effects for α-tocopherol [27].

Body weight

Female obesity and underweight are known to adversely affect fertility through alterations of hormone patterns and the menstrual cycle. Recent work investigating the effect of increasing maternal BMI on nitrative stress, antioxidant markers of oxidative stress, and protein oxidation in the placenta suggested that placental nitrative stress increased with maternal body weight, but was not associated with placental oxidative stress [28]. This unanticipated lack of increase in oxidative stress may be related to an interdependent relationship between formation of nitrative and oxidative stress; for example, ROS may be consumed by their reaction with reactive nitrogen species and thus nitrative stress effects increase while measures of protein carbonyls decrease. Obesity affects 30–75% of women with polycystic ovarian syndrome (PCOS) [29] and a number of studies have indicated that weight loss improves fertility among these women [30–32], although the effects of specific micronutrients and the possible role of oxidative stress represent a gap in the literature.

Smoking and alcohol

The adverse effects of smoking and alcohol on birth outcomes have been well documented, and growing evidence indicates that exposure to either can delay the time to conception possibly through increases in oxidative stress. Cigarette smoke contains a number of ROS, and metabolism of ethanol generates ROS through the electron transport chain, although other mechanisms related to subfertility and these exposures exist. A meta-analysis of 12 studies with strict inclusion criteria reported an odds ratio (OR) of 1.60 (95% CI 1.34–1.91) for infertility in female smokers compared with nonsmokers, with evidence of a dose-dependent relationship with the number of cigarettes smoked. Reduced fertility of smokers has also been documented among women undergoing IVF (OR =0.66, 95% CI 0.49–0.88) for pregnancies per number of IVF-treated cycles in smokers versus nonsmokers [33]. More recent evidence suggests exposure to secondhand smoke may adversely affect time to pregnancy. Among 225 female patients undergoing IVF (n =97) or IVF with intracytoplasmic sperm injection (ICSI; n =128), implantation rates of women exposed to passive smoke (as determined by self-report

of living with partner who smokes regularly) were similar to those of active smokers (12.6 and 12.0%, respectively) but significantly lower than those of nonsmoking women not exposed to passive smoke (25.0%, P <0.01). Pregnancy rates among active and passive smokers were also lower than those of nonsmokers (active smoker = 12.0%, passive smoker = 12.6%, and nonsmoker = 25.0%, P <0.001 for active versus nonsmoker and passive versus nonsmoker). Fertilization rate and embryo quality were similar across the three smoking categories [34]. Lower follicular fluid concentration of β-carotene and decreased IVF success have been documented among smokers [35], but no differences were seen in plasma concentrations of vitamin E or lycopene, suggesting that follicular loss of β-carotene occurs in response to tobacco-related oxidative stress. Both active and passive smoking may require increased antioxidant requirements [36,37].

In addition to the adverse effects of alcohol on established pregnancies, alcohol consumption may negatively impact time to pregnancy. Moderate alcohol consumption is associated with decreased concentration of plasma antioxidants and increased concentration of isoprostanes in postmenopausal women [38]. A similar increase in oxidative stress likely occurs among women trying to conceive as a combination of lipid peroxidation, protein oxidation, and DNA damage. A prospective study of 7393 Swedish women [39] concluded that women consuming at least two alcoholic drinks a day were at a significantly increased risk of infertility (RR = 1.58, 95% CI 1.07–2.34) and women consuming less than one alcoholic drink per day were at decreased risk [RR = 0.64, 95% CI 0.46–0.90 compared with moderate consumers of alcohol (>1 to <2 drinks per day)]. However, a prospective Danish Study [40] found increased risk of infertility with at least seven alcoholic drinks per week only among women of more than 30 years of age, suggesting that the effects of alcohol consumption may vary with age.

Caffeine

High levels of caffeine intake (>500 mg per day; approximately >5 cups per day) may increase time to pregnancy, as reported by a 45% increased risk of subfecundity (≥9.5 months to conception) in first pregnancies in the European Study of Infertility and Subfecundity [41]. A 2008 study reporting an increased risk of miscarriage among high consumers of caffeine [42] attracted some media attention, but the study has been criticized for potential recall bias among more than 50% of women who reported caffeine intake following miscarriage [43]. Another recent investigation failed to detect an association of caffeine intake and miscarriage among women with prospective reports of caffeine consumption [44].

Conclusion

Oxidative stress in the gynecologic environment is a likely mediator of conception but direct evidence is needed to confirm this hypothesis. Generation of ROS is a consequence of metabolically active cells, and it is likely that threshold levels of oxidative stress exist for promoting conception. The best available evidence suggests a varied diet with regular use of multivitamins, limited in caffeine and alcohol and maintenance of a healthy body weight may promote fertility. Prospective studies with dietary assessment and collection of biological samples before conception are needed to adequately evaluate the relationship between oxidative stress, dietary factors, and female fertility.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 296–297).

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