Antioxidants and Female Reproductive Function

Subjects: Obstetrics & Gynaecology

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Treatment with antioxidants is increasingly used to slow down aging processes in different organs of the human body, including those implicated in female fertility. There is a plethora of different natural, synthetic or semi-synthetic medicines available on the market; most of them can be purchased without medical prescription. Even though the use of antioxidants, even under conditions of auto-medication, was shown to improve many functions related to female infertility related to oxidative stress, the lack of medical control and supervision can lead to an overmedication resulting in an opposite extreme, reductive stress, which can be counterproductive with regard to reproductive function and produce various adverse health effects in general.

Keywords: aging ; antioxidant ; female fertility ; ovary ; oxidative stress

1. Ovarian Factor

1.1. Ovarian Factor in Young Women

Polycystic ovary syndrome (PCOS) and endometriosis are the leading ovarian causes of infertility in young women. Both PCOS and endometriosis are associated with oxidative stress [1].

Oxidative stress in PCOC patients is related to an increased serum prolidase activity, which also appears to be associated with increased cardiovascular risk and menstrual irregularities [2]. PCOS patients also show increased oxidative stress markers in follicular fluid and decreased oocyte and embryo quality [3], as well as a high level of chronic inflammation markers [4]. Little data are available as to the utility of externally administered antioxidants to reduce oxidative stress and improve fertility in PCOC patients (**Table 1**) [5]. The administration of an antioxidant cocktail containing vitamin A, vitamin B1, vitamin B6, vitamin B12, vitamin C, vitamin D3, vitamin E, nicotinamide, and folic acid significantly improved pregnancy rates in PCOS patients [6]. Two randomized controlled trials (RCTs) were performed with in vivo antioxidant treatment of PCOS patients, and they showed an improvement of oocyte and embryo quality after treatment with resveratrol [6], and an increase in implantation, pregnancy, and cumulative pregnancy rates after treatment with vitamins D and E [7], respectively (**Table 1**). Moreover, encouraging results were obtained in an animal model (rat) by using mitochondria-targeted antioxidant therapy [8]. Interestingly, administration of growth hormone (GH) during ovarian stimulation of young PCOS patients led to a significantly improved pregnancy, clinical pregnancy and spare embryo cryopreservation rate while reducing the total number of oocytes recovered and thus the patients' discomfort (**Table 1**) [9]. However, factors other than antioxidant actions could also have contributed to these GH effects.

Table 1. Antioxidants in the treatment of ovarian factor in young women.

Antioxidants	Pathology	Outcome	References
Resveratrol	PCOS	Improvement of oocyte and embryo quality	[5]
Vitamins D and E	PCOS	Increase in IR, PR, and CPR	[7]
Mixture of vitamin A, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin D3, vitamin E, nicotinamide, and folic acid	PCOS	Increase in PR	[6]
Growth hormone	PCOS	Increase in PR, CPR, and embryo cryopreservation rate	[9]
Vitamins C and E	Endometriosis	No effect on IVF outcome	[10]
Resveratrol	Endometriosis	Detrimental for IVF outcome	[11]

Abbreviations: PCOS: polycystic ovary syndrome; IR: implantation rate; PR: pregnancy rate; CPR: cumulative pregnancy rate; IVF: in vitro fertilization.

As to endometriosis, RCTs showed that in vivo treatment of patients with vitamins C and E reduced pelvic pain and decreased the concentration of peritoneal fluid inflammatory markers as compared with untreated patients (**Table 1**). The study failed to detect any positive effect of in vivo treatment of patients with endometriosis with vitamin C on in vitro fertilization (IVF) outcomes [10], while resveratrol supplementation during IVF cycles even appeared to be detrimental to pregnancy outcomes (**Table 1**) [11]. Further studies are needed to find out whether other combinations of antioxidant medicines could also improve IVF outcomes, in addition to reduce pain and inflammation, in patients with endometriosis.

1.2. Ovarian Factor in Older Women

Even though the causes of ovarian factor infertility present in young women usually persist until more advanced ages their relative importance decreases, while the main causes of infertility in older women are related to ovarian aging [12]. Diminished ovarian reserve (DOR), characterized by the decline in the quality and quantity of oocytes, is the most significant feature of ovarian aging and becomes the main reason for infertility and ART failure [12]. DOR is at the origin of primary ovarian insufficiency (POI) and can be accentuated by a variety of age-unrelated factors [12], including chromosome X structural abnormalities and X-autosome translocations [13], single-gene perturbations (some located on the X-chromosome and others on autosomes [14][15]), mendelian disorders implicated in other pathologies [14], mutations of genes (both nuclear and mitochondrial ones) affecting mitochondrial function [16][17], and disturbances of cell signaling pathways, especially those involved in cell protection against oxidative stress [18][19]. Independently of the exact cause, DOR and POI converge to mitochondrial damage, oxidative stress, and diminished ATP production, leading to inflammation, apoptosis, and telomere shortening [20], in addition to a decrease in the production of estradiol by the granulosa cells [21], a condition known to reduce oocyte developmental potential by causing an imbalance between nongenomic effects of androgens and estrogens at the oocyte surface [22].

In view of the above considerations, the use of antioxidants appears justified to improve oocyte quantity and quality in older women. Different antioxidants were tested in animal models of ovarian aging [23], and most of them gave encouraging results (**Table 2**). In mice, oral administration of vitamins C and E prevented the aging-related negative effects on ovarian reserve, metaphase II oocyte chromosomal aberrations and oocyte apoptosis in mice [22], N-acetyl-L-cystein mitigated age-related reduction of litter size and increased telomerase activity and telomere length [23], coenzyme Q10 restored oocyte mitochondrial function and fertility of aged animals [24], and melatonin improved age-induced fertility decline by attenuating ovarian mitochondrial oxidative stress [25]. Based on these encouraging data, different antioxidants were introduced into the treatment protocols used for ART in older women (**Table 2**). However, data obtained in humans are scarce and inconsistent, mainly because of the superimposition of different effects of the agents used, the heterogeneity of the patient populations studied, and the paucity of randomized controlled trials with appropriate controls.

Table 2. Antioxidants in the treatment of age-related ovarian factor.

Antioxidants	Species	Outcome	References
Vitamins C and E	Mouse	Protection of ovarian reserve Prevention of oocyte chromosomal aberrations and apoptosis	[23]
N-acetyl-L-cystein	Mouse	Increased litter size, telomerase activity, and telomere length	[24]
Coenzyme Q10	Mouse	Restoration of oocyte mitochondrial function Improvement of fertility	[25]
Melatonin	Mouse	Improvement of ovarian mitochondrial function and fertility	[26]
	Human	Recovery of pituitary function Improved oocyte quality and IVF outcomes	[27][28][29]
Growth hormone	Human	Improvement of DR and LBR	[28][29]
Growth hormone	Human	No effect in some women	[30]

Abbreviations: DR: delivery rate; LBR: live birth rate; IVF: in vitro fertilization.

An RCT performed in older women showed that the treatment of women aged >40 years with growth hormone resulted in an improvement of delivery and live birth rates [26]. Numerous subsequently published studies confirmed these findings and extended the use of growth hormone to other female infertility indications [27], including some younger women with

previous unexplained IVF failures [28][29][30][31]. Growth hormone was also shown to improve human oocyte in vitro maturation from the germinal vesicle to metaphase II stage [32]. On the other hand, growth hormone can also fail to improve IVF outcomes in some women, and several clues were suggested to distinguish those patients who would benefit from growth hormone treatment from those who would not [33]. Moreover, even though growth hormone is known to stimulate cell signaling pathways involved in the defense against oxidative damage [12], it is not known whether, and to what extent, this effect is responsible for the improvement of the oocyte developmental potential described in the above studies.

Melatonin was also used to improve reproductive function of aging women. In a randomized and placebo-controlled clinical study, the treatment of women 43–49 years old with melatonin for 6 months led to a significant decrement of serum FSH and LH levels, suggesting a recovery of pituitary function towards a more juvenile pattern of regulation [34]. The concentration of melatonin in the follicular fluid was shown to be positively correlated with antral follicle count, oocyte quality, and IVF outcomes [35][36]. A recent study, based on network pharmacology, demonstrated a multi-target mechanism of action of melatonin against DOR [37].

Antioxidants were also suggested to improve the corpus luteum function in animal models [38]. However, experience with the use of antioxidants to rescue the corpus luteum from premature luteolysis is still insufficient.

2. Uterine Factor

In the mouse model [39], the age-related decrease in uterine receptivity for embryo implantation was related to a redox imbalance that could be mitigated by intake of two different antioxidants, the nicotinamide adenine dinucleotide phosphate oxidase (NOX) inhibitor apocynin and the superoxide dismutase mimetic 4-hydroxy-2,2,6,6,-tetramethylpiperidinyloxy (TEMPOL). The former also significantly increased litter size and restored decidua thickness, while the latter increased birth weight, and both decreased protein carbonylation level in the uterus of reproductively aged mice [39]. Even though age-related decrease in the uterine and placental function were also described in some women, ART outcomes of aging women obtained with the use of oocytes from young donors are excellent [40], suggesting that uterine aging only represents a marginal problem in humans. Moreover, in a large cohort study, and after adjusting for age, no significant association between DOR and a short luteal phase was detected [41].

On the other hand some studies described age-unrelated problems of uterine receptivity leading to recurrent implantation failure (RIF). RIF usually refers to failure to achieve a clinical pregnancy after transfer of at least four good-quality embryos in a minimum of 3 fresh or frozen cycles in woman under the age of 40 years [41][42]. There is little information about the possible role of oxidative stress in the etiology of RIF. It was shown that co-treatment of women with the history of RIF with growth hormone during preparation for the transfer of embryos obtained with oocytes from young donors fertilized with normal sperm significantly improved embryo implantation, pregnancy, and live birth rates via beneficial actions on endometrial receptivity [43]. However, the mechanism of this growth hormone effect, including the question of whether and how this effect was mediated by the hormone antioxidant action, was not addressed.

3. Unexplained ART Failure Not Related to Age

Most of the studies related to the use of different antioxidants in the treatment of female infertility were carried out in cases of previous unexplained ART failures [44]. After exclusion of cases with poor semen quality, this group of patients can be subdivided into two subgroups: those showing poor oocyte and embryo quality and those with apparently normal oocytes and embryos.

In both conditions, the use of different antioxidants improved the outcomes in most, though not all cases (**Table 3**). A prospective cohort study [45] failed to demonstrate a significant improvement of ART outcomes after oral treatment of women with vitamin C during ovarian stimulation. Similarly, in an RCT using oral treatment with vitamin C for 14 days beginning with the day of oocyte retrieval, no improvement of implantation and clinical pregnancy rate was achieved [46]. As to vitamin E, another direct antioxidant agent, an observational study demonstrated a positive correlation of endogenous vitamin E concentrations in serum and follicular fluid with the number of metaphase II oocytes and some morphological parameters of embryo quality after IVF [47], but experience with therapeutic use of exogenous vitamin E is currently lacking.

More conclusive results were reported with the use of Coenzyme Q10 (CoQ10), a dual-role (pro-oxidant and antioxidant) molecule whose reduced form (ubiquinol) protects biological membranes from lipid peroxidation by recycling vitamin E and acting as an antioxidant [48]. In two RCTs, in vivo treatment of women with CoQ10 before the beginning of ovarian

stimulation was shown to result in lower aneuploidy rates in embryos generated by IVF [49] and higher numbers of large antral follicles and higher fertilization rates [50], respectively. However, the use of CoQ10 did not increase cumulative pregnancy rate and live birth rate as compared with controls [50]. On the other hand, an RCT evaluating the effects of the addition of CoQ10 to oocyte in vitro maturation (IVM) medium did not find any significant differences in the oocyte maturation and postmeiotic aneuploidy rates in oocytes from women <30 years old as compared with controls, while IVM in the presence of CoQ10 improved oocyte maturation and decreased blastocyst aneuploidy in women aged 38–46 years [51].

The use of resveratrol, a natural polyphenol of plant origin with antioxidant and anti-inflammatory properties, in women gave conflicting results. On the one hand, when added to IVM medium in an RCT, it increased the maturation rate and improved meiotic spindle morphology and chromosome arrangement in human oocytes cultured from the germinal vesicle to the methaphase II stage [52]. On the other hand, a retrospective study evaluating the in vivo effect of resveratrol added during the IVF cycle showed a diminished cumulative pregnancy rate and an increased miscarriage rate as compared to untreated women [53].

Two prospective cohort studies [54][55] and four RCTs [56][57][58][59] evaluated in vivo effects of melatonin administered from the cycle preceding the IVF attempt. It was shown that melatonin reduced the number of degenerated oocytes [54][59], increased the number of mature oocytes [56][59], and increased fertilization rate [55] and embryo quality [59]. One RCT [58] failed to detect any significant differences in cumulative pregnancy rate or oocyte and embryo parameters, but the authors recognized that the study was not sufficiently powered. Another RCT failed to demonstrate an effect of melatonin added to IVM medium on in vitro maturation of human germinal vesicle oocytes, although melatonin appeared to improve oocyte cytoplasmic maturation and subsequent IVF clinical outcome [60].

Table 3. Antioxidants in the treatment of age-unrelated ART failure.

Antioxidants	Type of Study	Outcome	References
Vitamin C	Prospective cohort	No effect on ART outcomes	[45]
	RCT	No improvement of IR and CPR in ART	[46]
Vitamin E	Observational, non-interventional	Positive correlation of serum and FF levels with oocyte maturity and embryo quality	[47]
Coenzyme Q10	RCT	Less aneuploidy in IVF embryos	[48]
	RCT	Increased FR No effect on CPR and LBR	[49]
Resveratrol	Retrospective	Decreased CPR	[52]
		Increased MR	[53]
Melatonin	Prospective cohort	Fewer degenerated oocytes	[54]
	Prospective cohort	Increased FR	[55]
	RCT	Improved oocyte and embryo quality	[58]

Abbreviations: ART: assisted reproduction technology; IR: implantation rate; CPR: cumulative pregnancy rate; IVF: in vitro fertilization; FF: follicular fluid; MR: miscarriage rate.

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