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22

Endometriosis and Infertility: The Role of Oxidative Stress

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1. Introduction

Several reports have supported the concept of reduced fecundity in women with endometriosis (Garrido et al., 2002; 2000). Contradictory data have been reported for in vitro fertilization (IVF) outcomes in patients with endometriosis (Garrido et al., 2002; Garcia-Velasco & Arici, 1999; Kumbak et al., 2008; Fernando et al., 2008). Some studies suggest lower fertilization, implantation, and pregnancy rates in women with endometriosis (Barnhardt et al., 2002; Al-Fadhli et al., 2006), possibly owing to impaired oocyte quality with consequent poor embryo quality, or to endometrial defects or defective interactions between the endometrium and the embryo (Kumbak et al., 2008, Brizek et al., 1995; Pellicer et al., 1995).

Oocyte quality depends on proper cytoplasmic and nuclear maturation (Kim et al., 1998), with the latter requiring the presence of normal cell spindles that guide chromosome segregation during meiosis (Wang & Keefe, 2002; Mandelbaum et al., 2004; De Santis et al., 2005; Volarcik et al., 1998; Van Blerkom & Davis, 2001). The cell spindle of the oocyte is extremely sensitive to several factors, including oxidative stress (Liu et al., 2003; Navarro et al., 2004; 2006), which might be involved in the etiopathogenesis of infertility related to endometriosis (Campos Petean et al, 2008; Mansour et al, 2009; Jozwik et al., 1999; Carbone et al., 2003).

The oxidative balance of the reproductive female tract depends on some types of free radicals and on different antioxidant mechanisms that neutralize them. There are two major groups of free radicals: reactive oxygen species and reactive nitrogen species.

2. Reactive Oxygen Species (ROS)

The ROS have physiological and pathological functions in the female reproductive tract. Fertility problems related to ROS have etiopathogenic factors in common (Agarwal et al., 2005). These reactive species are generated through enzymatic and non-enzymatic organic reactions. Biological reactions, through electron transference or through oxigenase, that use

oxygen (O_2) as substrate, generate large amounts of ROS. As the mithocondrial respiratory chain is the major O_2 cell intake system, the majority of ROS are produced by this system under physiological conditions (Fujii et al., 2005). The **superoxide radical (O_2^-)** is formed when electrons leak from the electron transport chain ($O_2 + e^- \rightarrow O_2^-$) (Agarwal et al., 2005). The dismutation of superoxide results in the formation of **hydrogen peroxide (H_2O_2)** ($2\ O_2^- + 2\ H^+ \rightarrow H_2O_2 + O_2$) (Agarwal et al., 2005). The same can also be generated by reduction of O_2^- ($O_2^- + e^- + 2\ H^+ \rightarrow H_2O_2$) (Babior, 1997). The **hidroxyl (OH^-) ion** is formed by the acquisition of 1 electron by **H_2O_2** ($H_2O_2 + e- + H^+ \rightarrow OH + H_2O$) (Babior, 1997). The hydroxyl ion is highly reactive and can modify purines and pyrimidines and cause strand breaks resulting in DNA damage (Agarwal et al., 2005).

3. Antioxidants

Under normal conditions, all organisms have enzymatic and non-enzymatic mechanisms capable of neutralizing pro-oxidants species and/or repair damages caused by reactive species, converting them to H_2O, to prevent overproduction. Many antioxidants of low molecular weight such as vitamins and polyphenols are usually found in nutrients, although enzymatic neutralization of reactive species is the most effective mechanism (Agarwal et al., 2005; Fujii et al., 2005).

4. Non-enzymatic antioxidants

Also known as synthetic antioxidants or dietary supplements, this group influences in an exogenous way the antioxidant defense system of the organism. The most common are: vitamins C and E, selenium, zinc, taurine, hypotaurine, glutathione, β-carotene, and carotene.

Vitamin E may block the initiation of lipid peroxidation as well as its propagation phase (Bornoden, 1994).

Glutathione is the major non-protein sulfhydryl component of mammalian cells and has an important role in cellular protection from oxidative stress (Meister, 1983). Glutathione synthesis increases throughout oocyte development and maturation until the periovulatory follicle stage (Perreault et al., 1988). After fertilization, glutathione participates in the sperm decondensation process, while the oocyte activation process occurs, and the sperm head turns into the male pronucleus (Calvin et al., 1986; Perreault et al., 1984, 1988; Yoshida, 1992, 1993). A study performed with bovine oocytes has shown the important role of COCs during the in vitro maturation process. Through gap junctions, cumulus oophorus cells (COCs) might mediate glutathione synthesis by the oocytes, a crucial enzyme for the cytoplasmic and nuclear maturation process. This intimate relation between COCs and oocytes apparently occurs due to the presence of gap junctions (De Matos et al., 1997).

5. Enzymatic antioxidants

The enzymatic defenses responsible for ROS neutralization are mainly represented by superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), depending or not on selenium and glutathione reductase (GR) (Fujii et al., 2005):

- **Superoxide dismutase (SOD):**

The superoxide anion is produced by a one-electron reduction of an oxygen molecule and initiates a radical chain reaction. It is believed that SOD, which dismutates the superoxide anion to hydrogen peroxide ($2\ O_2^- + 2\ H+ \rightarrow H_2O_2 + O_2$), plays a central role in antioxidant reactions. Three isozymes are produced by mammals (Fujii et al., 2005):

- SOD1 encodes Cu,Zn-SOD, which is largely cytosolic;
- SOD2 encodes Mn-SOD, a mitochondrial isoform;
- SOD3, which encodes the extracellular form (EC-SOD), structurally similar to CuZn-SOD.

One of the striking phenotypes of SOD1-deficient mice is female infertility, suggesting a potential role of this enzyme in female fertility. SOD2 is inducible under various oxidative stress and inflammatory conditions. EC-SOD is present at high levels in the epididymis, seminiferous tubules of the testis, as well as the lungs (Fujii et al., 2005).

The presence of SOD was evidenced in human follicular fluid (FF) and the identification of high concentrations of SOD in FF was associated with oocytes that were not fertilized (Sabatini et al., 1999). Data of a recently published study showed that SOD activity decreased with age in women, but increased in women with endometriosis and ovulatory dysfunction (Matos et al., 2009). When the cause of infertility was male factor, the success of ART was associated with increased SOD activity. Variations in SOD activity emphasize the importance of oxidative stress in the oocyte maturation process, and are suggested to be a potential biomarker of ART success (Matos et al., 2009).

A recent study has established a threshold level in FF which ROS may be considered toxic for viable embryo formation and pregnancy outcome. ROS, lipid peroxidation and total antioxidant capacity were estimated. The upper cut-off ROS level beyond which viable embryo formation is not favorable was found to be approximately 107 cps/400 microl FF. This level, determined in women with tubal factor infertility, was further validated in women with endometriosis and PCOS and correlated with fertilization and pregnancy rate and embryo quality (Jana et al., 2010).

- **Peroxidases:**

Catalase exclusively detoxifies hydrogen peroxide and has no requirement for an electron donor **($2\ H_2O_2 \rightarrow 2\ H_2O + O_2$)**. It plays a role in organs such as the liver, but its specific function in the genital tract is largely unknown (Fujii et al., 2005).

Glutathione is a tripeptidyl molecule and is present in either the reduced (GSH) or the oxidized state (GSSG). It plays pleiotropic roles, which include the maintenance of cells in a reduced state and the formation of conjugates with some harmful endogenous and xenobiotic compounds. In addition, GSH serves as an electron donor for GPx that reduces peroxide **($2GSH + H_2O_2 \rightarrow GSSG + 2\ H_2O$)**. At least four selenium-containing GPx isozymes are produced in mammals (Fujii et al., 2005):

The cytosolic form, GPX1, is widely distributed in tissues and has been the most extensively investigated form. However, GPX1-knockout mice show no abnormality in phenotype including reproductive capability (Ho et al., 1997);

- GPX2 encodes a gastrointestinal form, and no specific function for it is known in reproduction
- GPX3 is present in plasma and in epididymal fluid
- GPX4 encodes an isoform that specifically detoxifies phospholipid hydroperoxide and is thus referred to as PhGPx, and is expressed at high levels in the testis. A defect in GPX4 has been suspected to be a cause of male infertility triggered by selenium deficiency, although direct evidence for its requirement is missing (Hansen & Deguchi, 1996).

In a reaction promoted by peroxidase, GSH is oxidized to GSSG. Regeneration of GSH is, therefore, crucial for the ability of cells to fight exposure to oxidant metabolites. GSH levels are maintained by de novo synthesis that is catalyzed by two enzymes, γ- glutamylcysteine synthetase (γ-GCS) and glutathione synthetase (GS). The reduction of GSSG is catalyzed by **glutathione reductase** (GR) using NADPH as an electron donor **($2\ GSSG + NADPH + H^+ \rightarrow 2GSH + NADP^+$)**. GR is also inhibited by compounds produced in response to nitrosative stress, such as nitrosoglutathione. In the female reproductive system, GSH is assumed to play a role by reducing oxidative stress either by direct interaction with ROS, by the **glutathione redox system**, or by donating an electron to GPx (Fujii et al., 2005).

High levels of SeGPx were found in follicles that held oocytes with the potential to be fertilized and lower levels were related to fertilization failure (Paszkowski et al., 1995).

6. Endometriosis and oxidative stress

Some authors have suggested that endometriosis might be associated with oxidative stress (Agarwal et al., 2003; Szczepanska et al., 2003; Gupta et al., 2006). In pelvic endometriosis there might be an activation of macrophages in the peritoneal environment leading to increased production of reactive oxygen and nitrogen species, cytokines, prostaglandins, growth factors and, therefore, oxidative stress generating lipid peroxidation and its degradation products and other products formed by its interactions with low density lipoproteins and other proteins. Peroxidized lipids, when decomposed, generate products such as malondialdehyde (MDA) and could be recognized as foreign bodies, leading to an antigenic response with consequent production of antibodies (Halliwell, 1994; Murphy et al., 1998). This process would induce oxidative damage to red blood cells and to endometrial and peritoneal cells which would stimulate recruitment and activation of a larger number of mononuclear phagocytes, maintaining oxidative damage to the pelvic environment (Van Langendonckt et al., 2002). Oxidative stress compromises mesothelial cells and might induce adhesion sites for endometrial cells, contributing to development and progression of the endometriosis focus (Alpay et al., 2006).

In a recent study by our group, blood samples were collected during the early follicular phase of the menstrual cycle for the analysis of serum MDA, GSH and total hydroxyperoxide levels by spectrophotometry and of vitamin E by high performance liquid chromatography. A positive association between infertility related to endometriosis, advanced disease stage and increased serum hydroxyperoxide levels was demonstrated, suggesting an increased production of reactive species in women with endometriosis. These data, taken together with the reduction of serum vitamin E and GSH levels, suggest the

occurrence of systemic oxidative stress in women with infertility associated with endometriosis (Andrade et al., 2010).

The activation of polymorphonuclear leucocytes and macrophages observed in endometriosis patients might be induced by several factors, including damaged red blood cells, apoptotic endometrial cells, cellular debris and some other inflammatory cells. In endometriosis these actions of peritoneal macrophages appear to be stimulated *in vitro* by the immune response or by agents such as α and γ-interferon, increasing inducible nitric oxide synthase (NOS) expression, producing more nitric oxide and nitrite and nitrate compounds (Agarwal et al., 2005). However, we obtained no conclusive data concerning nitric oxide, peroxidized lipids and ROS levels in the peritoneal fluid of patients with and without endometriosis (Agarwal et al., 2003; Amaral et al., 2005).

In women with endometriosis and adenomyosis, we also observe a greater expression of Mn-SOD and CuZn-SOD in the endometrium throughout the menstrual cycle, as well as aberrant expression of GPx and xanthine peroxidase (XO), in topic and ectopic endometrium. SOD activity seems to be significantly higher in the ectopic endometrium of endometriomas than in the topic endometrium (Alpay et al., 2006). However, this increase in the expression of antioxidant enzymes in the topic and ectopic endometrium of endometriosis patients could be a primary event or secondary to an increase of ROS, which needs to be evaluated. If, on the one hand, we have no conclusive data concerning the pattern of expression of the most important oxidant and antioxidant enzymes in topic and ectopic endometrium, on the other hand, we have not found, so far, any studies that have evaluated the expression of these enzymes in granulosa cells of patients with endometriosis, whose anomalies could contribute to the impairment of folliculogenesis and of the acquisition of oocyte competence to permit fertilization and support embryo development.

The above data suggest a trend to a greater production of free radicals in endometriosis patients associated with a potential alteration of antioxidant capacity. This may contribute to oxidative stress which could be related to the pathogenesis and progression of endometriosis.

Another very interesting aspect of endometriosis is its enigmatic association with infertility, observed in 25 to 30% of women with this affection. Until now, little is known about the mechanisms involved in the pathogenesis of infertility, especially in minimal and mild endometriosis, where there is no significant alteration of pelvic anatomy.

New approaches to the treatment of infertility related to this disorder have included the increasingly more common application of ART. The introduction of *in vitro* fertilization (IVF) for the treatment of infertility secondary to endometriosis has become an important tool for the study of the potential effects of endometriosis on specific stages of the reproductive process, including folliculogenesis, fertilization, embryo development and implantation. Contradictory data have been reported for IVF outcomes in patients with endometriosis (García-Velasco & Arici, 1999; Garrido et al., 2000). This discrepancy seems to be multifactorial since IVF outcomes might be affected by different variables, such as ovulation induction protocol, patient selection criteria, laboratory procedures, and embryo transfer technique, among other factors.

As previously said, contradictory data have been reported for IVF outcomes in patients with endometriosis (Garrido et al., 2002; Garcia-Velasco & Arici, 1999; Kumbak et al., 2008; Fernando et al., 2008). Some studies suggest lower fertilization, implantation, and pregnancy rates in women with endometriosis (Barnhart et al., 2002; Al-Fadhli et al., 2006), possibly owing to impaired oocyte quality with consequent poor embryo quality, or to endometrial defects or defective interactions between the endometrium and the embryo (Kumbak et al., 2008, Brizek et al., 1995; Pellicer et al., 1995). Conflicting findings of some alterations in topic endometrium of endometriosis patients could explain, at least partially, the disturbance of the interaction between embryo and endometrium, generating anomalies in the implantation process (García-Velasco & Arici, 1999; Garrido et al., 2000). However, similar implantation rates in oocyte donation cycles have been recorded for women with endometriosis and control subjects, suggesting the crucial role of oocyte quality in impaired implantation processes (Pellicer et al., 1995; 2001; Díaz et al., 2000; Garrido et al., 2000; Katsoff et al., 2006). According to some authors, impaired oocyte quality would be responsible for compromising (Brizek et al., 1995) or completely blocking embryo development (Pellicer et al., 1995) in women with endometriosis, reinforcing the role of poor oocyte quality in the outcome of ART procedures in this group of patients.

Studies that intended to evaluate indirectly oocyte quality in patients with endometriosis analyzed multiple paracrine factors present in FF, such as interleukins, vascular endothelial growth factor (VEGF), and tumor necrosis factor (TNF), as well as granulosa cells apoptosis, leucocyte number and activity, among other indirect predictors of oocyte quality (Garrido et al., 2000, 2002). However, few studies have evaluated oocyte quality in patients with endometriosis by more objective morphological criteria.

Oocyte quality depends on factors related to the acquisition of nuclear and cytoplasmic competence. Although involving different processes, nuclear and cytoplasmic maturation are connected events that occur simultaneously in determined situations, although cytoplasmic molecular programming starts in the oocyte growth phase (Ferreira et al., 2009).

Nuclear competence depends on the anatomic and functional integrity of the meiotic spindle, a temporary and dynamic structure responsible for chromosomal segregation during meiosis (Wang & Keefe, 2002; Navarro et al., 2005). Meiotic anomalies might contribute to cell development failure by different paths, such as the inability of the oocyte to complete the maturation process in order to be fertilized, or the occurrence of variable errors of the meiotic maturation process that do not stop fertilization but might compromise embryo development pre or post implantation, as well as the future viability of the fetus (Armstrong, 2001; Chaube et al., 2005; Mansour et al., 2009). On the other hand, there is evidence that oxidative stress might promote meiotic anomalies and pre-implantation embryo development (Liu et al., 2003; Navarro et al., 2004, 2006; Agarwal et al., 2006; Mansour et al., 2009). Oxidative stress also seems to induce genomic and mitochondrial DNA damage (Aitken et al., 2001), which leads directly to reduced fertility (Guerin et al., 2001). Recently it was demonstrated that the peritoneal fluid of endometriosis patients promotes anomalies in oocyte cytoskeleton and increases embryo apoptosis, preventable by antioxidant supplementation (L-carnitine) in the culture medium, as shown in a study using mice as the experimental model (Mansour et al., 2009), suggesting that oxidative stress

might be involved in the etiopathogenesis of poor oocyte quality in patients with this disease. In some recent studies, sperm incubated with peritoneal fluid of endometriosis patients showed increased DNA fragmentation and the extent of fragmentation increased according to endometriosis stage and infertility duration. Similarly, oocytes incubated with peritoneal fluid of endometriosis patients presented increased DNA damage and the extent of damage was proportional to the period of exposure. As expected, embryos incubated with peritoneal fluid also showed DNA fragmentation as indicated by an increase of apoptosis. The increase of DNA damage in spermatozoa, oocytes and embryos seems to be responsible for the numerous abortions and for fertilization and implantation failure among endometriosis patients (Mansour et al., 2009).

Our group was the first to assess the meiotic spindle and chromosome distribution of in vitro–matured (IVM) oocytes obtained from stimulated cycles of endometriosis patients and to compare them with a control group consisting of couples with male or tubal factors of infertility. We showed that, although IVM rates were similar for the two groups evaluated, a higher proportion of telophase I oocytes tended to occur in the endometriosis group. The number of oocytes was too low to detect statistically significant differences. However, this finding suggests a potential delay or impairment of meiosis I during IVM in the context of endometriosis. The mechanisms underlying this finding remain unclear. Recent studies demonstrated significant DNA damage and increased anomalies in the microtubules and chromosomes of oocytes incubated with PF from endometriosis patients (Mansour et al, 2009; Carbone et al., 2003), which were prevented by supplementation of the culture medium with the antioxidant L-carnitine, suggesting that impaired oocyte quality in endometriosis may be mediated by oxidative stress (Carbone et al., 2003). Although the data were obtained from frozen/thawed MII mouse oocytes and may not necessarily be extrapolated to human oocytes, they support our hypothesis that oxidative stress might be involved in the delay or impairment of meiosis I in oocytes of women with endometriosis (Barcelos et al., 2009), a possibility that requires more in-depth evaluation in future studies.

Unpublished data from our group suggest that this finding is also confirmed in in vivo matured oocytes of patients with moderate and severe endometriosis. However, we did not find well designed studies evaluating different pro and antioxidants markers in this group of patients, co-relating them with ART outcome as indirect predictors of oocyte quality.

If we have very little evidence correlating endometriosis and meiotic oocyte anomalies, data about the potential association between endometriosis and oocyte cytoplasmic maturation markers are even rarer. The gene expression of the antioxidant enzymatic system is one of the markers of oocyte cytoplasmic maturation, playing an important role by minimizing the hazardous effects of oxidative stress (Cetica et al., 2001). It has already been demonstrated that catalase, SOD and GPx are found in oocytes and COCs. GSH is one of the oocyte cytoplasmic maturation markers that have been intensely investigated. Some studies show that an adequate expansion of COCs, which is considered to be an oocyte maturation marker, is partially dependent on the intracellular concentration of GSH (Furnus et al., 1998). Intracellular GSH levels increase as the oocyte develops from germinal vesicle to metaphase II (Ali et al., 2003). After fertilization, the total amount of intracellular GSH correlates with spermatic chromatin decondensation, with consequent oocyte activation and

also with the transformation of the sperm head to male pronucleus (De Matos & Furnus, 2000). However, no studies have evaluated the expression of this enzyme or of the entire GSH redox system in COCs of patients with infertility related to endometriosis. Matos et al. (2009) suggested a positive correlation between the SOD activity of COCs of infertile women submitted o ovarian stimulation for ART due to male factor and ART outcomes. In this same study an increase in SOD activity was observed in in vitro culture of COCs from infertile women with endometriosis. However, the authors analyzed the COCs of only six patients.

Some authors have associated minimal endometriosis with impaired steroidogenesis in granulosa cells, represented not only by a reduced baseline activity of aromatase, but also by a lower production of progesterone in non-stimulated and stimulated cycles (Harlow et al., 1996; Gomes et al., 2008). A functional failure of oocytes due to abnormal follicular function could be a result of this disease (Wardle et al., 1985). The antioxidants not only have an anti-apoptotic effect on preovulatory in vitro cultured follicles (Tsai-Turton & Luderer, 2006), but are also involved in the regulation of steroidogenic enzyme function dependent on cytochrome P450 (Verit et al., 2007). Some studies have suggested that ascorbic acid (Murray et al., 2001), as well as SOD (Lapolt & Hong, 1995) may have inhibitory effects on aromatase, an enzyme responsible for the conversion of androgens to estrogens, which could induce storage of androgens in the follicular fluid, leading to follicular atresia (Verit et al., 2007). As mentioned earlier, some recent data have demonstrated an increase of SOD activity in COCs (in vitro culture) of infertile women with endometriosis (Matos et al., 2009). Since no studies on endometriosis patients have evaluated antioxidant enzyme expression in luteinized granulosa cells and their correlation with steroidogenic enzymes dependent on cytochrome P450 expression, involved in ovarian steroidogenesis, our group has performed studies evaluating these possible associations.

7. Endometriosis, steroidogenesis and folliculogenesis

Some studies have shown an increase of luteinized unruptured follicle syndrome (LUF) and of the incidence of lutheal phase defects in women with endometriosis (Cheesman et al., 1983; Holtz et al., 1985; Saracoglu et al., 1985; Kaya & Oral, 1999). Other recent studies have shown a polymorphism of the progesterone gene and resistance to the action of progesterone in endometriosis tissues (Bulun et al., 2006; Van Kaam et al., 2007), supporting the hypothesis of impaired progesterone production and/or action in endometriosis (Bulun et al., 2006; Harlow et al., 1996). Some data show impaired steroidogenesis of granulosa cells associated with minimal endometriosis, represented not only by a reduction of basal aromatase activity, but also by a lower production of progesterone in stimulated as well as non-stimulated cycles (Harlow et al, 1996). Therefore, ovulatory dysfunction induced by impairment of ovarian steroid secretion as well as inadequate lutheal function might be important for the pathogenesis of infertility associated with endometriosis. A function defect in the oocyte due to abnormal follicle function might be the result of this ovulatory dysfunction (Wardle et al., 1985). Supporting this hypothesis, clinical studies involving IVF and some programs of oocyte donation have pointed out the importance of impaired oocyte quality in the pathogenesis of infertility associated with endometriosis (Pellicer et al., 1998; Garrido et al., 2002).

3β-Hydroxysteroide dehydrogenase/delta 5-delta 4-isomerase (3β-HSD) is an important enzyme associated with the biosynthesis of progesterone. Bar Ami (1994) evaluated the fertilization capacity related to the competence of granulosa cells and COCs to secrete progesterone. COCs from fertilized oocytes presented a 1.9 times higher progesterone level ($p<0.001$) on days 0-3 and a 1.6 times higher level ($p<0.02$) on days 3-5 of culture when compared to the levels in COCs of non-fertilized oocytes. Nevertheless, in COCs of fertilized oocytes, the activity of 3β-hydroxysteroid dehydrogenase was significantly higher after oocyte aspiration and also 3 to 5 days later compared to non-fertilized oocytes. These results suggest that, in stimulated cycles, in follicles that hold mature COCs there is a synchrony and correlation between competence to perform progesterone secretion by COCs as well as by granulosa cells and the potential of these oocytes to be fertilized. Such correlation suggests and supports the intimate relation of enzymatic activity of 3β-hydroxysteroid dehydrogenase and progesterone production with oocyte fertilization capacity, which may suggest the important role of this enzyme as coadjuvant in the acquisition of oocyte competence. The reduction of the gene expression and/or activity of this enzyme could lead to a lower production of progesterone and impairment of the lutheal phase.

Aromatase is present in granulosa cells and actually plays a fundamental role in follicle maturation and in the establishment of oocyte quality (Erickson et al., 1989; Foldesi et al., 1998; Speroff & Fritz, 2005). But, if on the one hand we find evidence of increased aromatase expression in ectopic endometrium, on the other, there are poor and inconclusive data concerning the expression of this enzyme by luteinized granulosa cells, suggesting a lower activity of this enzyme, but with no confirmation of an associated lower gene expression.

It is known that oocyte quality results from a complex and synchronized process that lasts several months, from primordial follicle to pre-ovulatory follicle. This process starts in a gonadotropin-independent way and later becomes gonadotropin dependent. In this last phase, oocyte, granulosa cells and FSH interact synergically. Granulosa cell multiplication and the specific way they respond first to FSH and later to LH in order to produce intra-follicle steroids are crucial events in this process (Speroff & Fritz, 2005). We know that there are gap junctions between granulosa cells, which is evidence that there are molecular interactions between them and possibly with the oocyte itself, through signaling molecules such as growth and differentiation factor-9 (GDF-9) and bone morphogenetic protein-15 (BMP 15) (Albertini & Barrett, 2003; Combelles et al., 2004; Thomas & Vanderhyden, 2006; Hutt & Albertini, 2007). However, little information is available about the communication between granulosa cells and the oocyte.

Granulosa cells differentiate into mural and cumulus cells during folliculogenesis, a fact that has stimulated the study of their potential as mesenchymal stem cells. To date there are no studies comparing the gene expression of mural granulosa cells and COCs and, possibly, since they are cells with distinct function and differentiation, there might be genes with different patterns of expression. When they reach the pre-antral follicle stage, granulosa cells can synthetize all three types of steroids (androgens, progestagens and estrogens) (Speroff & Fritz, 2005). However, the proportions and timing of their production are crucial. It is known that FSH and also LH have hormonal receptors on granulosa cells and there is a synergism between these receptors and intra-follicle hormonal production to permit the

development of a follicle that holds a mature oocyte (Costa et al., 2004; Speroff & Fritz, 2005; Silva et al., 2008). Androgens, for instance, are necessary at low concentrations at the very beginning of follicle development, as a substrate for estradiol production. According to the two cells theory, theca cells convert C21 components (cholesterol) to androgen, which is a substrate for the aromatase of granulosa cells that converts androgens (C19) to estrogens (C18). The transformation of an androgenic environment to an estrogenic one is crucial in order to produce an oocyte capable of ovulation (Speroff & Fritz, 2005). In granulosa cells, aromatase plays an essential role in folliculogenesis and in estradiol production and its expression increases with follicle development (Tetsuka &Hillier, 1997; Guet et al., 1999) under the influence of FSH (Speroff & Fritz, 2005). Therefore, aromatase is a crucial enzyme in granulosa cells which is responsible for the formation of an estrogenic follicle microenvironment, essential for development and maturation (Speroff & Fritz, 2005). Nevertheless, it is important to state that aromatase is the final point of the entire ovarian steroidogenic cascade and the only enzyme capable of converting androgens to estrogens. Therefore, if its activity is impaired, that specific follicle will have difficulty in acquiring a normal pre-ovulatory state.

Intra-follicle hormonal relations are essential for the success of the entire ovulatory process both in natural cycles and in cycles stimulated for ART. Regarding maturation, Costa et al. (2004) analyzed cycles stimulated with exogenous gonadotropins without using a GnRH analogue and found that the follicles that held mature oocytes presented an increase in the progesterone/testosterone (P/T) ratio), in the progesterone/estradiol (P/E2) ratio and in the estradiol/testosterone (E/T) ratio in follicular fluid when compared to immature oocytes, suggesting a decrease in C21 to C19 conversion, but not in aromatase activity. Silva et al. (2008) analyzed these same ratios in follicles of women submitted to stimulated cycles using a GnRH analogue and observed that the action of the analogue remained intact and its most important effect was a decrease in intra-follicle androgen, with higher rates of fertilization and maturation.

In vitro studies using granulosa cell culture of women with endometriosis submitted to ovarian hyperstimulated cycles showed that these cells present impaired aromatase activity. Harlow et al. (1996) investigated aromatase activity in patients with minimal and mild endometriosis using granulosa cell culture in which estrogen production was evaluated after adding testosterone to the culture medium. They found a decrease in aromatase activity in patients with endometriosis compared to control. Researchers from the same group (Cahill et al., 2003) using the same technique found a lower sensitivity to LH in granulosa cells of patients with endometriosis.

Abreu et al. (2006) found a reduction of estradiol production in *in vitro* luteinized mural granulosa cells of women with endometriosis, after 24 hours of cell culture. Under baseline conditions or when the culture medium was supplemented with a lower concentration of testosterone ($2x10^{-6}M$), estradiol production was lower in the endometriosis group. However, when the concentration of testosterone (an aromatase precursor) added to the culture medium was increased ($2x10^{-5}M$), there was no difference between the endometriosis and control groups concerning estradiol production. In another study performed by Abreu et al. (2009) no difference in aromatase gene expression (CYP19A1) was observed in luteinized mural cells of women with endometriosis and controls submitted to

ART. However, data obtained by the analysis of gene expression of mural granulosa cells of patients with endometriosis cannot be necessarily extrapolated to cumulus oophorus cells (COCs).

We found evidence that COCs might contribute to oocyte cytoplasmic maturation (Tanghe et al., 2002) through a net of gap junctions between COCs and between these and the oocyte (Furger et al., 1996). Nevertheless, the presence of COCs is important for fertilization to occur (Tanghe et al., 2002) because it attracts selected spermatozoa and promotes their capacitation and penetration. On the other hand, it should be emphasized that COCs protect the oocyte against apoptosis induced by oxidative stress (Tatemoto et al., 2000), which occurs when there is a large number of ROS compared to the anti-oxidants available. Some studies have suggested that analysis of gene expression of COCs might be used as an indirect predictor of oocyte quality and of the outcome of ART procedures, which could lead to distinct clinical applications (Hamamah et al., 2006; Assou et al., 2006, 2008; Hamel et al., 2008; Tesfaye et al., 2009; Haouzi & Hamamah, 2009).

In the female reproductive system, ROS and anti-oxidants play physiological roles during folliculogenesis, oocyte maturation, lutheal regression and fertilization (Agarwal et al., 2006). For example, an increase in ROS production in granulosa cells (Jancar et al., 2007) and on oxidative damage to DNA marker (8-hydroxy-20-deoxyguanosine) levels in granulosa cells and COCs (Seino et al., 2002) was associated with lower fertilization, poor embryo quality and reduction of implantation rates. Nevertheless, oxidative stress also seems to be associated with the etiopathogenesis of reproduction, as is the case in endometriosis (Guerin et al., 2001; Van Langendonckt et al., 2002; Agarwal et al., 2003; Barcelos et al., 2008), idiopathic infertility and polycystic ovary syndrome (Gonzalez et al., 2006).

Considering this substantial involvement of ROS and oxidative stress in fertilization and reproduction modulation, it is accepted that anti-oxidant enzymes on COCs modulate oocyte maturation and might be related to specific conditions that limit the success of ART. Some studies have shown that superoxide dismutase (La Polt & Hong, 1995) might have inhibitory effects on aromatase, suggesting a potential correlation between gene expression of one of the major anti-oxidant enzymatic system and aromatase expression.

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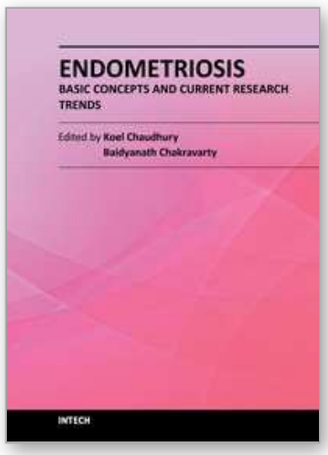

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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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