Cell Tissue Res (2016) 364:1–7
DOI 10.1007/s00441-015-2339-9

REVIEW

Oxidative stress and oocyte quality: ethiopathogenic mechanisms of minimal/mild endometriosis-related infertility

Michele Gomes Da Broi[1] · **Paula Andrea Navarro**[1]

Received: 18 September 2015 / Accepted: 23 November 2015 / Published online: 19 December 2015

Abstract Endometriosis, a highly prevalent gynecological disease, is often associated with infertility, even in its milder forms (minimal and mild endometriosis). However, no consensus has been established with regard to this relationship and the possible mechanisms involved have not been completely elucidated. The oocyte is believed to have an important role in the infertility presented by these patients. Hence, oxidative stress events associated with alterations in the peritoneal, serum and/or follicular microenvironments might result in poor oocyte quality and compromise the reproductive potential of these women. Here, we review possible mechanisms involved in oocyte quality impairment that might lead to infertility in patients with early endometriosis.

Keywords Early endometriosis · Infertility · Oocyte quality · Oxidative stress · Follicular microenvironment

Endometriosis and infertility

Endometriosis, a gynecological disease characterized by implantation and growth of endometrial tissue (glands and stroma) outside the uterine cavity (Gupta et al. 2006), is a highly prevalent disease present in 10–15 % of women of reproductive age (Augoulea et al. 2012; Singh et al. 2014). It can be asymptomatic or accompanied by symptoms such as chronic pelvic pain, dysmenorrhea and dyspareunia and is also frequently associated with infertility (Bellelis et al. 2010; Signorile and Baldi 2010; Singh et al. 2014). In this last-mentioned context, an estimated 30–50 % of women with the disease are infertile and 25–50 % of infertile women are diagnosed with endometriosis (Practice Committee of the ASRM 2012).

The association between endometriosis and infertility is well established in the literature (Garrido et al. 2000; Giudice and Kao 2004; Gupta et al. 2008). The monthly fecundity rate in normal couples of reproductive age is knwon to be 15–20 %, whereas the rate in infertile women with endometriosis ranges from 2 to 10 % (Hughes et al. 1993). However, the association between infertility and early-stage disease (minimal endometriosis [stage I] and mild endometriosis [stage II]), in which no substantial pelvic anatomical changes are identified, remains controversial (Akande et al. 2004; Bergqvist and D'Hooghe 2002). The most relevant studies investigating cumulative rates of natural pregnancy in women with early endometriosis, subjected or not to surgical treatment (adhesiolysis and cauterization of endometriosis foci) during laparoscopy performed by experienced surgeons, highlight the deleterious impact of the disease on female fertility (Marcoux et al. 1997; Parazzini 1999). In these studies, only women with infertility exclusively associated with early endometriosis, as diagnosed by laparoscopy, were eligible; cases involving ovulatory disorders, tubal obstruction, or changes in semen quality were excluded. The most intriguing finding of these studies is that, even when the surgical treatment improves the natural fertility (Marcoux et al. 1997), the cumulative rate of pregnancy in women with early endometriosis remains substantially lower (expectant management: 22.5 % (Marcoux et al. 1997) and 19.6 % (Parazzini 1999) or surgical treatment: 37.5 % (Marcoux et al. 1997) and

✉ Michele Gomes Da Broi
michi.dabroi@gmail.com

[1] Human Reproduction Division, Department of Obstetrics and Gynecology, Ribeirão Preto School of Medicine, University of São Paulo, 3900, Avenida Bandeirantes, Ribeirão Preto, SP 14049-900, Brazil

22.2 % (Parazzini 1999)) than that in fertile women (~80 %; Gnoth et al. 2003).

Although the results of the aforementioned studies can be considered to reinforce the proposal regarding the deleterious impact of early endometriosis on natural fertility, the questions remain as to whether infertility in these patients is truly associated with the presence of early endometriosis or whether it might be related to other, as yet unidentified, infertility factors (unexplained infertility, also termed UI). Akande et al. (2004) compared cumulative pregnancy rates and live births in 75 patients diagnosed with endometriosis I/II (EI/II) and 117 patients with UI during the 3 years following the completion of diagnostic laparoscopy and found that the probability of pregnancy over this period is significantly lower in the group with early endometriosis (35.5 %) than in patients with UI (54.6 %), suggesting that infertility in early-stage endometriosis and UI are two distinct entities, with early endometriosis possibly being a female infertility factor.

Role of oocyte quality

The mechanisms that might be involved in the etiopathogenesis of endometriosis-related infertility, especially in stages I and II, are little understood, despite being the subject of numerous recent studies. In this context, some authors have suggested that infertility in women with the disease might be attributable to compromised oocyte quality, thus reflecting embryo and/or endometrial defects or interactions between the endometrium and the embryo (Brizek et al. 1995; Kumbak et al. 2008; Pellicer et al. 1995). Studies on oocyte donation cycles have reinforced the role of oocyte quality in infertile patients with the disease (Garcia-Velasco and Arici 1999; Garrido et al. 2000). In a retrospective study, Simon et al. (1994) assessed outcomes of ovodonation cycles and observed similar implantation and pregnancy rates in women who presented with and without endometriosis and who received oocytes from donors without the disease. However, implantation rates were significantly lower in women without endometriosis who received oocytes from women with endometriosis. These findings suggest that oocyte changes in patients with the disease lead to poorer quality embryos with a lower likelihood of implantation. Likewise, Sung et al. (1997) retrospectively reviewed data for oocyte recipients who presented with and without endometriosis and who received oocytes donated by women without the disease and observed no differences in implantation (28 % vs. 29 %) or pregnancy (12 % vs. 13 %) rates between recipients with and without endometriosis; this also suggests a role of impaired oocytes and, consequently, embryonic quality in the disease-related infertility. However, these studies, in addition to being retrospective, evaluated small case series, limiting their generalizability and reinforcing the need for further studies investigating potential underlying pathological mechanisms. An understanding of these mechanisms is fundamental for the development of new therapeutic approaches for improving the natural fertility of women with endometriosis-related infertility. Our group has invested considerable research efforts in this topic with the use of both human oocytes and an experimental bovine model.

The acquisition of oocyte competence is known to depend on adequate cytoplasmic and nuclear maturation, the latter being dependent on the presence of a normal spindle (Albertini 1992; Ferreira et al. 2009). The meiotic spindle of human oocytes in metaphase II, a temporary and dynamic structure composed of microtubules, is associated with the oocyte cortex and its subcortical microfilaments network (Kim et al. 1998; Mandelbaum et al. 2004; Wang and Keefe 2002) and is essential to ensure the fidelity of chromosome segregation during meiosis (De Santis et al. 2005; Van Blerkom and Davis 2001; Volarcik et al. 1998). The meiotic spindle, however, is extremely sensitive to the action of various factors (Eichenlaub-Ritter et al. 2002; Hu et al. 2001; Mullen et al. 2004), such as oxidative stress, which can promote meiotic abnormalities and chromosome instability, increase apoptosis and impair the development of the preimplantation embryo (Liu et al. 2003; Navarro et al. 2004, 2006). Results of an investigation of the cell spindle and chromosome distribution of in-vitro-matured oocytes obtained from infertile women with endometriosis suggest that meiosis I is potentially delayed or compromised in these patients, supporting a relationship between endometriosis and oocyte meiotic abnormalities (Barcelos et al. 2009).

Oxidative stress

Given that endometriosis is associated with chronic inflammation and that reactive oxygen species (ROS) are inflammatory mediators known to modulate cell proliferation (Gupta et al. 2008), some authors have suggested that endometriosis is associated with oxidative stress (Agarwal et al. 2003; Carvalho et al. 2012; Gupta et al. 2008; Szczepanska et al. 2003), with an etiopathogenesis that might be related to an inflammatory response to ectopic endometrial implants (Murphy et al. 1998). Thus, endometriotic cells might promote oxidative stress by increasing ROS production, altering detoxification pathways, and/or decreasing the levels of catalase, such as occurs in tumor cells (Ngo et al. 2009). In the female reproductive tract, ROS might act physiologically and, under normal conditions, are involved in functions such as cell signaling, oocyte maturation, ovarian steroidogenesis (Agarwal et al. 2005), ovulation (Shkolnik et al. 2011), luteal function, luteolysis, gametic interaction and embryonic metabolism (Agarwal et al. 2005). The trend toward the increased production of free radicals in women with endometriosis

associated with a potential change in antioxidant capacity has been suggested to contribute to the occurrence of oxidative stress, which, in turn, might be related to the disease and its progression (Agarwal et al. 2003; Gupta et al. 2006; Szczepanska et al. 2003).

In the context of pelvic endometriosis, macrophages are believed to be activated in the peritoneal cavity, potentially promoting the increased production of ROS and reactive nitrogen species, cytokines, growth factors and prostaglandins. The resulting oxidative stress causes lipid peroxidation and further generates products resulting from its degradation or formed by its interaction with low-density lipoproteins and other proteins. Decomposition of peroxidized lipid generates products such as malondialdehyde that might be recognized as foreign bodies, triggering an antigenic response with the consequent production of antibodies (Halliwell 1994; Murphy et al. 1998). This process culminates in oxidative damage to erythrocytes and peritoneal endometrial cells, which, in turn, stimulates further recruitment and activation of mononuclear phagocytes, perpetuating the oxidative damage to the pelvic cavity (Van Langendonckt et al. 2002). Oxidative stress might also damage mesothelial cells and induce the appearance of adhesion sites for endometrial cells by promoting the development and progression of endometriosis (Alpay et al. 2006).

Peritoneal fluid

A study by Mansour et al. (2009) demonstrated that peritoneal fluid (PF) from women with endometriosis promotes microtubule and chromosome abnormalities in mature mouse oocytes, in addition to increasing embryonic apoptosis. These anomalies are reduced by supplementation of the medium with the antioxidant L-carnitine, suggesting that substances present in the PF of women with this disease compromise oocyte and embryo quality, with oxidative stress being a likely mediator. However, these authors included, among their PF donors, both women with pelvic pain and infertile women with endometriosis and did not assess the impact of the disease stage or the role of PF during ovarian folliculogenesis. In this regard, our preliminary data evaluating the role of PF from infertile women with minimal or mild pelvic endometriosis show a lower expression of *CAT* and *GSH* genes, encoding important antioxidant enzymes, in bovine oocytes that were in-vitro-matured in the presence of PF from infertile women with EI/II compared with PF from fertile women (Navarro et al. 2013). These findings suggest that substances present in the PF of women with early endometriosis compromise ovarian folliculogenesis, promoting oocyte oxidative damage. Our group also evaluated the effect of PF from fertile women and infertile women with EI/II on nuclear maturation and meiotic anomalies of in-vitro-matured bovine oocytes, providing evidence that PF from infertile women with EI/II exerts a deleterious effect on cell spindle and chromosome distribution. These results suggest that alterations in the peritoneal microenvironment of infertile women with early endometriosis undermines maturation and oocyte quality (Jianini et al. 2014).

Follicular fluid and serum

Whereas the follicular microenvironment plays a critical role in oocyte maturation, changes in the composition of the follicular fluid (FF) might influence oocyte quality, affecting fertilization, early embryonic development and subsequent pregnancy (Ma et al. 2010). FF is a metabolically active microenvironment containing steroid hormones, growth factors, cytokines, ROS and antioxidants, among other factors, produced by granulosa cells, endothelial cells and leukocytes (Attaran et al. 2000; Pasqualotto et al. 2004). Although ROS are important for some female reproductive tract functions, including their essential role in the ovulatory response (Shkolnik et al. 2011), when in excess (and possibly accompanied by an inadequate antioxidant response) they might have a negative impact, especially on estradiol (E2) levels, which are an important predictor of the ovarian response (Appasamy et al. 2008), damaging steroidogenesis and consequently oocyte maturation and ovulation (Agarwal et al. 2003; Al-Fadhli et al. 2006).

Differences in the FF composition between women with and without endometriosis have been reported (Campos Petean et al. 2008; Garrido et al. 2000; Gupta et al. 2008; Jackson et al. 2005), suggesting that FF affects the acquisition of oocyte competence in women with endometriosis. Our group investigated whether oxidative stress in the follicular microenvironment is involved in female infertility. In these studies, we compared five oxidative stress markers in FF from infertile women undergoing controlled ovarian stimulation for intracytoplasmic sperm injection (ICSI). Results showed higher total antioxidant capacity (TAC) levels in FF from women who failed to become pregnant, suggesting that oxidative stress in this microenvironment is associated with worse ICSI outcomes (Da Broi et al. 2013).

In another study, we compared the levels of eight oxidative stress markers in FF and the serum of infertile women with and without endometriosis undergoing controlled ovarian stimulation for ICSI. Results showed higher serum concentrations of the antioxidants glutathione and superoxide dismutase, lower serum TAC concentrations, higher concentrations of follicular 8-hydroxy-2′-deoxyguanosine (8OHdG; an indicator of oxidative DNA damage) and higher follicular vitamin E levels in infertile women with endometriosis compared with those without the disease. These findings suggest that the presence of systemic and follicular oxidative stress in this group of patients is related to the impairment of oocyte quality, revealing a possible mechanism in disease-related infertility (Da Broi et al. 2014a). A comparison of the same eight

markers in serum and FF from infertile women with endometriosis I/II and those without the disease revealed higher serum concentrations of total hydroperoxides (measured by FOX-1 assays and an indicator of ROS production), lower serum TAC concentrations and higher follicular 8OHdG concentrations in the endometriosis group, demonstrating that systemic and follicular oxidative stress is also present in women with minimal and mild endometriosis and might be involved in the infertility exhibited by patients with early disease (Da Broi et al. 2014c).

Our group also evaluated the effect of FF from infertile women with mild endometriosis on nuclear maturation and meiotic oocyte anomalies during in vitro maturation of bovine oocytes and reported that FF from infertile women with mild disease possibly compromised nuclear maturation and the meiotic spindles of these oocytes (Da Broi et al. 2014b). These findings led us to hypothesize that oxidative stress in the follicular microenvironment affects nuclear maturation and promotes meiotic oocyte abnormalities in infertile women with endometriosis. To test this, we conducted a follow-up study in which we assessed the role of FF from infertile women with mild endometriosis in the genesis of meiotic anomalies and evaluated the potential protective effect of adding antioxidants (L-carnitine and N-acetylcysteine) to the culture medium in in-vitro-matured bovine oocytes. We found a detrimental effect of FF from infertile women with mild disease on spindle and chromosomal distribution but this effect was diminished or completely prevented by the addition of antioxidants, especially L-carnitine (Giorgi et al. 2015). These findings suggest that oxidative stress is involved in worsening oocyte quality in women with mild endometriosis and open new perspectives onto the pathogenic mechanisms of infertility related to early disease.

Cumulus cells

One way indirectly to assess oocyte quality is to analyze markers in cumulus cells (CCs). During follicular development, the granulosa cells differ in the mural population, limiting the follicular antrum and in the CC population, which

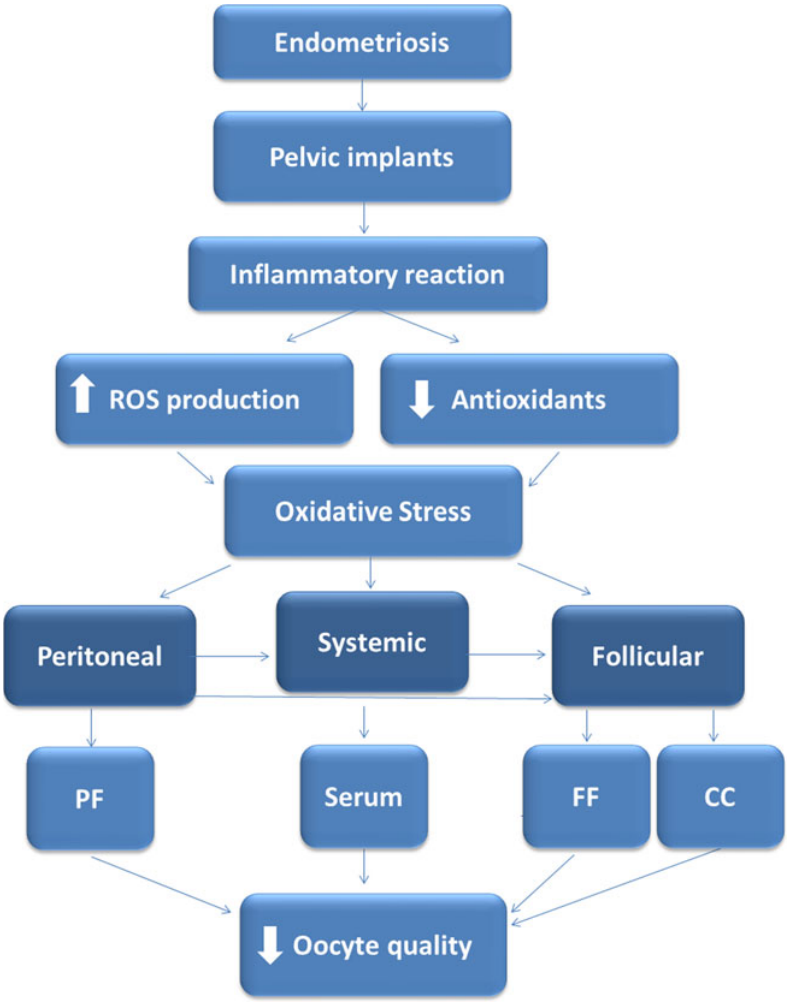

Fig. 1 Oxidative stress and oocyte quality: possible ethiopathogenic mechanism involved in minimal/mild endometriosis-related infertility (*ROS* reactive oxygen species, *PF* peritoneal fluid, *FF* follicular fluid, *CC* cumulus cells)

surrounds the oocyte. Mural cells are responsible for estrogen production and rupture of the follicle, whereas CCs are intimately associated with oocyte development. CCs are regulated, in part, by factors derived from the oocyte, while contributing to oocyte maturation and development potential (Eppig et al. 2002; Tanghe et al. 2002). In this context, some studies have suggested that the analysis of gene expression in CCs can be used as an indirect predictor of oocyte quality and outcomes of assisted reproduction technologies, with possible clinical applications (Hamel et al. 2008; Haouzi and Hamamah 2009; Tesfaye et al. 2009).

Studies have been performed to compare the expression of genes related to folliculogenesis, acquisition of oocyte competence and oxidative stress in CCs of infertile women with and without endometriosis. Because aromatase plays an essential role in follicular steroidogenesis and successful pregnancy, Barcelos et al. (2015) compared the expression of the aromatase-encoding gene, *CYP19A1*, in CCs of infertile women with and without endometriosis undergoing controlled ovarian stimulation for ICSI and found that the expression of *CYP19A1* is lower in CCs of infertile women with endometriosis compared with CCs of controls. The evaluation of this gene in CCs of early endometriosis patients undergoing controlled ovarian stimulation for ICSI also showed the lower expression of *CYP19A1* in the endometriosis group (Ferriani et al. 2013). These studies suggest that reduced expression of the *CYP19A1* gene in CCs is involved in impaired follicular steroidogenesis and the worsening of oocyte quality in infertile women with endometriosis, even in early-stage disease.

Because the induction of *CYP19A1* is possibly mediated by increased cyclooxygenase-2 (COX-2), Donabela et al. (2011) evaluated the expression of the *PTGS2* gene encoding COX-2 in the CCs of endometriosis and control groups and revealed lower *PTGS2* expression in patients with endometriosis. This finding might be related to the reduced expression of aromatase in the CCs of these women, a suggestion that will require confirmation by future studies.

Concluding remarks

No consensus has been reached regarding the association between early-stage pelvic endometriosis and infertility. Whether the initial stages of the disease really affect natural fertility or are only incidental findings in some patients with UI is also unclear. However, the studies presented here reinforce the crucial role of minimal and mild endometriosis in female infertility and show that the disease significantly affects the cumulative pregnancy rates of these women, even for those undergoing surgery. Despite the fact that surgical treatment (adhesiolysis and cauterization of endometriosis foci) significantly improves pregnancy rates, it does not completely restore these women's reproductive potential, which remains substantially lower than that of fertile women and women with UI. Many pathological mechanisms are potentially involved in the infertility associated with early disease. Studies investigating oocytes, CCs, serum, PF and FF in early-stage disease in humans and in animal models have suggested that impaired oocyte quality is an important factor underling the infertility of these women. Because endometriosis is associated with chronic inflammation and ROS generation, the trend toward the increased production of ROS in women with endometriosis, associated with a potential change in antioxidant capacity, might contribute to the occurrence of oxidative stress. The oxidative stress in the peritoneal microenvironment might be reflected in the systemic compartment and possibly affects the follicular microenvironment, compromising oocyte quality and, consequently, the reproductive potential of these patients (Fig. 1).

These data open new perspectives for an understanding of the pathogenic mechanisms involved in early disease-related infertility and for the design of future studies to investigate novel therapeutic approaches for improving the natural fertility of these women. As such, they could have major implications for clinical practice, since access to in vitro fertilization technology is limited, even in developed countries.

References

Agarwal A, Saleh RA, Bedaiwy MA (2003) Role of reactive oxygen species in the pathophysiology of human reproduction. Fertil Steril 79:829–843

Agarwal A, Gupta S, Sharma RK (2005) Role of oxidative stress in female reproduction. Reprod Biol Endocrinol 3:28

Akande VA, Hunt LP, Cahill DJ, Jenkins JM (2004) Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis. Hum Reprod 19:96–103

Albertini DF (1992) Cytoplasmic microtubular dynamics and chromatin organization during mammalian oogenesis and oocyte maturation. Mutat Res 296:57–68

Al-Fadhli R, Kelly SM, Tulandi T, Tanr SL (2006) Effects of different stages of endometriosis on the outcome of in vitro fertilization. J Obstet Gynaecol Can 28:888–891

Alpay Z, Saed GM, Diamond MP (2006) Female infertility and free radicals: potential role in adhesions and endometriosis. J Soc Gynecol Investig 13:390–398

Appasamy M, Jauniaux E, Serhal P, Al-Qahtani A, Groome NP, Muttukrishna S (2008) Evaluation of the relationship between follicular fluid oxidative stress, ovarian hormones, and response to gonadotropin stimulation. Fertil Steril 89:912–921

Attaran M, Pasqualotto E, Falcone T, Goldberg JM, Miller KF, Agarwal A, Sharma RK (2000) The effect of follicular fluid reactive oxygen species on the outcome of in vitro fertilization. Int J Fertil Womens Med 45:314–320

Augoulea A, Alexandrou A, Creatsa M, Vrachnis N, Lambrinoudaki I (2012) Pathogenesis of endometriosis: the role of genetics, inflammation and oxidative stress. Arch Gynecol Obstet 286:99–103

Barcelos ID, Vieira RC, Ferreira EM, Martins WP, Ferriani RA, Navarro PA (2009) Comparative analysis of the spindle and chromosome configurations of in vitro-matured oocytes from patients with endometriosis and from control subjects: a pilot study. Fertil Steril 92: 1749–1752

Barcelos ID, Donabella FC, Ribas CP, Meola J, Ferriani RA, Paz CC de, Navarro PA (2015) Down-regulation of the CYP19A1 gene in cumulus cells of infertile women with endometriosis. Reprod Biomed Online 30:532–541

Bellelis P, Dias JA Jr, Podgaec S, Gonzales M, Baracat EC, Abrao MS (2010) Epidemiological and clinical aspects of pelvic endometriosis—a case series. Rev Assoc Med Bras 56:467–471

Bergqvist A, D'Hooghe T (2002) Mini symposium on pathogenesis of endometriosis and treatment of endometriosis-associated subfertility. Introduction: the endometriosis enigma. Hum Reprod Update 8:79–83

Brizek CL, Schlaff S, Pellegrini VA, Frank JB, Worrilow KC (1995) Increased incidence of aberrant morphological phenotypes in human embryogenesis—an association with endometriosis. J Assist Reprod Genet 12:106–112

Campos Petean C, Ferriani RA, Reis RM dos, Moura MD de, Jordao AA Jr, Navarro PA (2008) Lipid peroxidation and vitamin E in serum and follicular fluid of infertile women with peritoneal endometriosis submitted to controlled ovarian hyperstimulation: a pilot study. Fertil Steril 90:2080–2085

Carvalho LF, Samadder AN, Agarwal A, Fernandes LF, Abrao MS (2012) Oxidative stress biomarkers in patients with endometriosis: systematic review. Arch Gynecol Obstet 286:1033–1040

Da Broi MG, Andrade AZ, Rodrigues JK, Paz CCP, Jordão AA, Navarro PA (2013) Total antioxidant capacity (TAC) levels in follicular fluid of infertile patients undergoing ICSI: a possible predictor of clinical pregnancy. IFFS/ASRM Conjoint Meeting. Fertil Steril 100:S425

Da Broi MG, Albuquerque FO, Andrade AZ de, Cardoso RL, Jordão AA Jr, Navarro PA (2014a) Systemic and follicular oxidative stress in infertile women with endometriosis undergoing controlled ovarian stimulation for ICSI: is there a role in the ethiopathogenesis of infertility? Fertil Steril 102:e79

Da Broi MG, Malvezzi H, Paz CC, Ferriani RA, Navarro PA (2014b) Follicular fluid from infertile women with mild endometriosis may compromise the meiotic spindles of bovine metaphase II oocytes. Hum Reprod 29:315–323

Da Broi MG, Rodrigues JK, Andrade AZ, Giorgi VSI, Jordão AA, Navarro P (2014c) Systemic and follicular oxidative stress in infertile women with minimal/mild endometriosis undergoing controlled ovarian stimulation for ICSI: is there a role in the etiopathogenesis of infertility? JBRA Assist Reprod 18:117

De Santis L, Cino I, Rabellotti E, Calzi F, Persico P, Borini A, Coticchio G (2005) Polar body morphology and spindle imaging as predictors of oocyte quality. Reprod Biomed Online 11:36–42

Donabela F, Barcelos I, Pavdovan C, Meola J, Ferriani RA, Navarro P (2011) PTGS2 gene expression (COX2) in cummulus oophorus cells of endometriosis and control infertile patients submitted to ICSI. ASRM 67th Annual Meeting. Fertil Steril 96: S236–S237

Eichenlaub-Ritter U, Shen Y, Tinneberg HR (2002) Manipulation of the oocyte: possible damage to the spindle apparatus. Reprod Biomed Online 5:117–124

Eppig JJ, Wigglesworth K, Pendola FL (2002) The mammalian oocyte orchestrates the rate of ovarian follicular development. Proc Natl Acad Sci U S A 99:2890–2894

Ferreira EM, Vireque AA, Adona PR, Meirelles FV, Ferriani RA, Navarro PA (2009) Cytoplasmic maturation of bovine oocytes: structural and biochemical modifications and acquisition of developmental competence. Theriogenology 71:836–848

Ferriani RA, Barcelos I, Donabela F, Ribas C, Meola J, Navarro PA (2013) Lower expression of the gene CYP19A1 in cumulus oophorus cells from infertile women with minimal and mild endometriosis may be involved in the infertility related to this disease. 5th International IVI Congress, Seville, Spain. http://comtecmed.com/ivi/2013/Uploads/Editor/abstract_41.pdf

Garcia-Velasco JA, Arici A (1999) Is the endometrium or oocyte/embryo affected in endometriosis? Hum Reprod 14(Suppl 2):77–89

Garrido N, Navarro J, Remohi J, Simon C, Pellicer A (2000) Follicular hormonal environment and embryo quality in women with endometriosis. Hum Reprod Update 6:67–74

Giorgi VS, Da Broi MG, Paz CC, Ferriani RA, Navarro PA (2015) N-acetyl-cysteine and L-carnitine prevent meiotic oocyte damage induced by follicular fluid from infertile women with mild endometriosis. Reprod Sci (in press)

Giudice LC, Kao LC (2004) Endometriosis. Lancet 364:1789–1799

Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G (2003) Time to pregnancy: results of the German prospective study and impact on the management of infertility. Hum Reprod 18:1959–1966

Gupta S, Agarwal A, Krajcir N, Alvarez JG (2006) Role of oxidative stress in endometriosis. Reprod Biomed Online 13:126–134

Gupta S, Goldberg JM, Aziz N, Goldberg E, Krajcir N, Agarwal A (2008) Pathogenic mechanisms in endometriosis-associated infertility. Fertil Steril 90:247–257

Halliwell B (1994) Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet 344:721–724

Hamel M, Dufort I, Robert C, Gravel C, Leveille MC, Leader A, Sirard MA (2008) Identification of differentially expressed markers in human follicular cells associated with competent oocytes. Hum Reprod 23:1118–1127

Haouzi D, Hamamah S (2009) Pertinence of apoptosis markers for the improvement of in vitro fertilization (IVF). Curr Med Chem 16: 1905–1916

Hu Y, Betzendahl I, Cortvrindt R, Smitz J, Eichenlaub-Ritter U (2001) Effects of low O_2 and ageing on spindles and chromosomes in mouse oocytes from pre-antral follicle culture. Hum Reprod 16: 737–748

Hughes EG, Fedorkow DM, Collins JA (1993) A quantitative overview of controlled trials in endometriosis-associated infertility. Fertil Steril 59:963–970

Jackson LW, Schisterman EF, Dey-Rao R, Browne R, Armstrong D (2005) Oxidative stress and endometriosis. Hum Reprod 20:2014–2020

Jianini BTGM, Giorgi VSI, Malvezzi H, Da Broi MG, Paz CCP da, Navarro PAAS (2014) Peritoneal fluid from infertile women with minimal/mild endometriosis may compromise the spindle of metaphase II bovine oocytes. 8th Annual Congress of the SBRA. JBRA Assist Reprod 18:117–118

Kim NH, Chung HM, Cha KY, Chung KS (1998) Microtubule and microfilament organization in maturing human oocytes. Hum Reprod 13:2217–2222

Kumbak B, Kahraman S, Karlikaya G, Lacin S, Guney A (2008) In vitro fertilization in normoresponder patients with endometriomas: comparison with basal simple ovarian cysts. Gynecol Obstet Invest 65: 212–216

Liu L, Trimarchi JR, Navarro P, Blasco MA, Keefe DL (2003) Oxidative stress contributes to arsenic-induced telomere attrition, chromosome instability, and apoptosis. J Biol Chem 278:31998–32004

Ma CH, Yan LY, Qiao J, Sha W, Li L, Chen Y, Sun QY (2010) Effects of tumor necrosis factor-alpha on porcine oocyte meiosis progression, spindle organization, and chromosome alignment. Fertil Steril 93: 920–926

Mandelbaum J, Anastasiou O, Levy R, Guerin JF, Larouziere V de, Antoine JM (2004) Effects of cryopreservation on the meiotic spindle of human oocytes. Eur J Obstet Gynecol Reprod Biol 113 (Suppl 1):S17–S23

Mansour G, Abdelrazik H, Sharma RK, Radwan E, Falcone T, Agarwal A (2009) L-carnitine supplementation reduces oocyte cytoskeleton

damage and embryo apoptosis induced by incubation in peritoneal fluid from patients with endometriosis. Fertil Steril 91:2079–2086
Marcoux S, Maheux R, Berube S (1997) Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. N Engl J Med 337:217–222
Mullen SF, Agca Y, Broermann DC, Jenkins CL, Johnson CA, Critser JK (2004) The effect of osmotic stress on the metaphase II spindle of human oocytes, and the relevance to cryopreservation. Hum Reprod 19:1148–1154
Murphy AA, Santanam N, Morales AJ, Parthasarathy S (1998) Lysophosphatidyl choline, a chemotactic factor for monocytes/T-lymphocytes is elevated in endometriosis. J Clin Endocrinol Metab 83:2110–2113
Navarro PA, Liu L, Keefe DL (2004) In vivo effects of arsenite on meiosis, preimplantation development, and apoptosis in the mouse. Biol Reprod 70:980–985
Navarro PA, Liu L, Ferriani RA, Keefe DL (2006) Arsenite induces aberrations in meiosis that can be prevented by coadministration of N-acetylcysteine in mice. Fertil Steril 85 (Suppl 1):1187–1194
Navarro PA, Malvezzi H, Da Broi MG, Rosa e Silva JC, Vireque AA, Meola J (2013) The peritoneal fluid of infertile women with and without minimal/mild endometriosis reduces the expression of genes GSR and CAT in bovine oocytes. 5th International IVI Congress, Seville, Spain. http://comtecmed.com/ivi/2013/Uploads/Editor/abstract_88.pdf
Ngo C, Chereau C, Nicco C, Weill B, Chapron C, Batteux F (2009) Reactive oxygen species controls endometriosis progression. Am J Pathol 175:225–234
Parazzini F (1999) Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Hum Reprod 14:1332–1334
Pasqualotto EB, Agarwal A, Sharma RK, Izzo VM, Pinotti JA, Joshi NJ, Rose BI (2004) Effect of oxidative stress in follicular fluid on the outcome of assisted reproductive procedures. Fertil Steril 81:973–976
Pellicer A, Oliveira N, Ruiz A, Remohi J, Simon C (1995) Exploring the mechanism(s) of endometriosis-related infertility: an analysis of embryo development and implantation in assisted reproduction. Hum Reprod 10 (Suppl 2):91–97
Practice Committee of the ASRM (2012) Endometriosis and infertility: a committee opinion. Fertil Steril 98:591–598
Shkolnik K, Tadmor A, Ben-Dor S, Nevo N, Galiani D, Dekel N (2011) Reactive oxygen species are indispensable in ovulation. Proc Natl Acad Sci U S A 108:1462–1467
Signorile PG, Baldi A (2010) Endometriosis: new concepts in the pathogenesis. Int J Biochem Cell Biol 42:778–780
Simon C, Gutierrez A, Vidal A, de los Santos MJ, Tarin JJ, Remohi J, Pellicer A (1994) Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum Reprod 9:725–729
Singh N, Lata K, Naha M, Malhotra N, Tiwari A, Vanamail P (2014) Effect of endometriosis on implantation rates when compared to tubal factor in fresh non donor in vitro fertilization cycles. J Hum Reprod Sci 7:143–147
Sung L, Mukherjee T, Takeshige T, Bustillo M, Copperman AB (1997) Endometriosis is not detrimental to embryo implantation in oocyte recipients. J Assist Reprod Genet 14:152–156
Szczepanska M, Kozlik J, Skrzypczak J, Mikolajczyk M (2003) Oxidative stress may be a piece in the endometriosis puzzle. Fertil Steril 79:1288–1293
Tanghe S, Van Soom A, Nauwynck H, Coryn M, Kruif A de (2002) Minireview: functions of the cumulus oophorus during oocyte maturation, ovulation, and fertilization. Mol Reprod Dev 61:414–424
Tesfaye D, Ghanem N, Carter F, Fair T, Sirard MA, Hoelker M, Schellander K, Lonergan P (2009) Gene expression profile of cumulus cells derived from cumulus-oocyte complexes matured either in vivo or in vitro. Reprod Fertil Dev 21:451–461
Van Blerkom J, Davis P (2001) Differential effects of repeated ovarian stimulation on cytoplasmic and spindle organization in metaphase II mouse oocytes matured in vivo and in vitro. Hum Reprod 16:757–764
Van Langendonckt A, Casanas-Roux F, Donnez J (2002) Oxidative stress and peritoneal endometriosis. Fertil Steril 77:861–870
Volarcik K, Sheean L, Goldfarb J, Woods L, Abdul-Karim FW, Hunt P (1998) The meiotic competence of in-vitro matured human oocytes is influenced by donor age: evidence that folliculogenesis is compromised in the reproductively aged ovary. Hum Reprod 13:154–160
Wang WH, Keefe DL (2002) Prediction of chromosome misalignment among in vitro matured human oocytes by spindle imaging with the PolScope. Fertil Steril 78:1077–1081