Endometriosis and oocyte quality: the role of ROS

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ABSTRACT

Background: Endometriosis is one of the most prevalent gynecological diseases in fertile women. It is characterized by the implantation and dissemination of functional endometrial tissue in ectopic positions. It is currently considered one of the main causes of infertility and a main reason for the use of assisted reproduction techniques (ART). Endometriosis-related infertility could be explained by a chronic inflammatory process and oxidative stress occurring at various levels (peritoneal fluid, follicular fluid, uterine endometrium).

Purpose: The aim was to compare the clinical results of ART treatment between a group of patients with endometriosis and a control group (women with tubal infertility).

Methods: This was a retrospective observational cohort study; we evaluated 28 assisted reproductive protocols (14 in the endometriosis group and 14 in the control group) performed between October 2018 and March 2019 at the Center of Infertility and Assisted Reproduction, Department of Clinical and Experimental Medicine, University of Pisa. In each woman, clinical aspects were assessed: antral follicle counts (AFC) and levels of anti-Müllerian hormone (AMH), follicle-stimulating hormone, estrogens and progesterone at induction of ovulation, UI of gonadotropin, and stimulation duration. To assess some parameters, the patients with endometriosis were divided in two subgroups:

- patients with deep infiltrating endometriosis, who underwent surgery before treatment with ART (number of patients=8)
- patients who did not undergo surgery before treatment with ART (number of patients=6)

Results: The control group had significantly higher AMH and AFC levels and used a lower dose of gonadotropin (the significance, in both cases, increased when considering the endometriosis-surgery subgroup). Moreover, there emerged a significant difference in the percentage of grade I embryos (66% in control group vs 26% in endometriosis group).

Conclusion: In women with endometriosis the results of treatment with ART are not yet satisfactory. In fact, in these patients the problem is the inflammatory microenvironment, which affects the reproductive process. Only by understanding and interrupting these mechanisms might ART outcomes be improved.

KEYWORDS

Endometriosis; oxidative stress; infertility; inflammation; oocyte quality.

Introduction

Endometriosis is one of the most common female diseases. It is defined as the dissemination and growth of functional endometrial tissue (glands and stroma) outside the uterine cavity [1]. Endometriosis should actually be considered a heterotopia in which the ectopic endometrium is influenced by hormonal stimuli (in particular estrogenic) and cyclically proliferates, becomes a secretory tissue and breaks down, just as the endometrial mucosa does [2].

This estrogen-dependent condition affects women of reproductive age, and it is associated with chronic pelvic pain and infertility.

The prevalence of the disease is difficult to estimate accurately because the diagnosis is still based on laparoscopic view and histological analysis of the lesions [3]. At present, there are no serum markers or imaging techniques able to replace the role of laparoscopy in this setting. In spite of this, the estimation of prevalence ranges between 10 and 15%, but in some specific subgroups is higher [4,5]:

- 30-50% in women with infertility [6]
- 10-25% in women undergoing treatment with assisted reproductive techniques (ART) [7]
- 30-80% in women with chronic pelvic pain [6-9].

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Endometriosis and infertility

Endometriosis is considered one of the causes of infertility even though a causal link has never been demonstrated. In women with endometriosis, infertility is much more frequent (30-50%) [6], the monthly fecundity rate drops to 2-10% [10], the chance of getting pregnant is lower than in the general population (36% vs 55%)[11], ovarian reserve and oocyte quality are worse, and even when treated with ART these women have greater difficulty conceiving and maintaining pregnancy [12].

In the presence of severe endometriosis, infertility can be explained by the anatomical changes in the pelvic cavity. Instead, in the minimal and mild stages of the disease, it is much more difficult to explain the reason for infertility.

Endometriosis and inflammation

Endometriotic lesions, with their cyclical modification, are responsible for an inflammatory microenvironment. This is a vicious circle in which endometrial tissue produces inflammation, the inflammation recruits inflammatory/immune cells, which then enhance the inflammation itself. The inflammation is associated with hyperproduction of inflammatory cytokines, prostaglandins, proteases, and chemokines, and causes the production of reactive oxygen species (ROS) [13-15].

Physiologically, the body has antioxidant systems (enzymatic or non-enzymatic) which can protect against oxidative stress. However, in women with endometriosis, because of the chronic inflammatory microenvironment, these systems are depleted. There is a loss of balance between protective and damage systems involved in oxidative stress [16, 17].

The oxidative stress has an impact at various levels [14]:

- peritoneal fluid
- follicular fluid
- uterine endometrium

Many studies have demonstrated increased concentrations of prostaglandins, pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, tumor necrosis factor alpha and angiogenic cytokines such as IL-8 and vascular endothelial growth factor in the peritoneal and follicular fluid of women with endometriosis [18-23].

In Jianini's experimental model [24], bovine oocytes exposed to peritoneal fluid from women with endometriosis were compared with oocytes exposed to peritoneal fluid from a group of controls. Meiotic spindle and nuclear maturation disorders were found to be more frequent in oocytes exposed to "endometriotic fluid". Cohen *et al*. [25] did the same with Mus musculus oocytes, finding a lower number of normal oocytes in the endometriotic group, with far more abnormalities. Furthermore, Malvezzi *et al*. [26] analyzed the gene expression of superoxide dismutase-1 (SOD1) in bovine oocytes kept in contact with three different concentrations (1, 5, 10%) of peritoneal fluid from women with minimal or mild endometriosis. The oocytes in the 10% group showed significantly lower expression of SOD1 than those in the control group (0.67 ± 0.32 vs 1.06 ± 0.22).

These three experimental models demonstrate that the inflamed peritoneal fluid of women with endometriosis could damage oocyte quality.

Follicular fluid surrounds oocytes, so it is a key factor throughout the maturation process of the oocyte. In women with endometriosis, because of the inflammatory disorders, it negatively affects oocyte development, reducing both the quality of the oocytes and sperm fertilization [27].

Da Broi *et al*. [28] compared oxidative stress markers in follicular fluid and in serum from women with minimal or mild endometriosis with the same markers measured in controls. Women with endometriosis displayed a higher serum level of total hydroperoxides (8.48 ± 1.72 vs 7.69 ± 1.71 µmol/g protein), a lower serum level of total antioxidant capacity (0.38 ± 0.18 vs 0.46 ± 0.15 mEq Trolox/L) and a higher follicular fluid level of 8-hydroxy-2'–deoxyguanosine (24.21 ± 8.56 vs 17.22 ± 5.6 ng/ml). This means that women with endometriosis show peritoneal, systemic and follicular oxidative stress.

In this way, oxidative stress seems to compromise oocyte quality and embryo quality, and, in general, the reproductive potential of "endometriotic" women [29]. Oxidative stress could be at the root of the problems encountered in women with endometriosis. It would be interesting to understand how oxidative stress acts at different reproductive levels in order to investigate new therapeutic strategies and improve fertility.

With this aim our study set out to analyze the actual weight of ROS in influencing oocyte quality, by assessing clinical aspects, i.e. antral follicle counts (AFC), levels of Anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), estrogens and progesterone at induction of ovulation, UI of gonadotropin and stimulation duration; and biological aspects, i.e. the number of retrieved, inseminated and fertilized oocytes and the quality of embryos obtained. To support our study, we also considered literature data, such as those reported by Da Broi *et al*. [28].

Materials and Methods

We analyzed 28 assisted reproductive protocols performed at the Center of Infertility and Assisted Reproduction of the Department of Clinical and Experimental Medicine, University of Pisa, between October 2018 and March 2019. Sixteen patients underwent ART treatment because of endometriosis. Two of these patients were excluded because they did not complete the stimulation protocol. The control group comprised 14 patients with tubal factor infertility (Table 1). The patients with endometriosis were divided in two subgroups (Table 1):

- patients with deep infiltrating endometriosis who underwent surgery before treatment with ART (number of patients=8)
- patients who did not undergo surgery before ART treatment (number of patients=6)

All patients underwent a complete clinical history and physical examination, biochemical analyses, and transvaginal ultrasonography. In particular we recorded:

- mean age
- weight (Kg)
- height (cm)
- body mass index, BMI (Kg/m^2)
- basal FSH
- AMH
- AFC

Table 1 Patients included in the study.

ENDOMETRIOSIS STUDY		
Endometriosis group (N°14)		Control group
Surgery (N° patients 8)	NO surgery (N° patients 6)	(N° patients 14)
Total number of patients, 28 / Total number of cycles, 28		

Patients aged between 18 and 43 years and affected by endometriosis or tubal factor infertility were included in the study, while patients with other associated female infertility factors such polycystic ovary syndrome, premature ovarian failure, with other endocrine diseases, or aged over 43 years were excluded from the study. Patients with severe oligoasthenospermia in their male partner were also excluded from the study.

Acccording to the protocol of the ethics committee of Area Vasta Nord Ovest (Pisa, Italy), due to the observational, retrospective nature of the study, formal approval was not required.

Results

We analyzed 28 patients divided into an endometriosis group and a control group. The data analysis is summarized in Table 2. There was no significant difference in age, weight, height and BMI between the two groups.

This means that the two populations are superimposable with regard to these parameters. Conversely, the AFC and AMH values were significantly higher in the control group (AFC 15.20 ± 3.83 in the control group vs 9.54 ± 2.76 in the endometriosis group, p=0.03; AMH 3.02 ± 1.22 in the control group vs 1.43 ± 0.73 in the endometriosis group, p=0.03). On analyzing the AFC and AMH values in the control group and in the two subgroups of endometriosis patients (surgery and no surgery), we found significant differences between both the control group and the endometriosis-surgery subgroup and between the control group and the endometriosis-no surgery subgroup (Table 3). In particular, AMH was significantly higher in the control group than in the endometriosis-surgery subgroup (3.02 ± 1.22 vs 1.18 ± 0.56, p=0.005) and in the control group than in the endometriosis-no surgery subgroup (3.02 ± 1.22 vs 1.67 ± 0.81, p=0.04). With regard to AFC, the control group women had significantly more antral follicles than the women in the endometriosis-no surgery subgroup (15.20 ± 3.83 vs 10.17 ± 1.94, p=0.04) and the women in the endometriosis-surgery subgroup (15.20 ± 3.83 vs 9 ± 3.37, p=0.01).

Conversely, no significant difference in FSH was measured.

To evaluate stimulation response in the endometriosis and control groups, we considered:

- Total gonadotropin dose
- Cycle stimulation duration
- Estrogen and progesterone levels at ovulation induction
- Number of follicles >16 mm at ovulation induction
- Number of retrieved oocytes at pick-up
- Number of inseminated oocytes
- Number of fertilized oocytes
- Number of embryos, considering embryo quality (grades I, II, III)
- Percentage total embryos/fertilized oocytes

There emerged significant differences (Table 4) between the endometriosis and control groups in:

- The total dose of gonadotropin used to induce superovulation (2010 ± 801.7 in the control group vs 2970 ± 878.8 in the endometriosis group, p=0.04),
- The number of follicles >16 mm at ovulation induction (6.40 ± 2.30 in the control group vs 4.14 ±1.87 in the endometriosis group, p=0,02),
- The number of grade I embryos obtained with ART (1.67 ± 1.03 in the control group vs 0.42 ± 0.65 in the endometriosis group, p=0.02).

Comparing the percentages of grade I, II and III embryos

Table 2 Features of the control group and the endometriosis group; [1]p=0.03.

	CONTROL GROUP AVERAGE ± SD	ENDOMETRIOSIS GROUP AVERAGE ± SD
N° patients	14	14
N° cycles	14	14
Age (years)	35.67 ± 3.9	35.79 ± 3.7
Weight (kg)	62.5 ± 12.6	58.5 ± 7.5
Height (m)	168 ± 4.4	163.2 ± 5
BMI (kg/m^2)	22.21 ± 4.9	21.98 ± 2.9
FSH	8.2 ± 1.8	8.9 ± 3.2
AMH	3.02 ± 1.22	1.43 ± 0.73 [1]
AFC	15.20 ± 3.83	9.54 ± 2.76 [1]

AMH: Anti-Müllerian hormone; AFC: Antral follicle count; FSH: Follicle stimulating hormone

Table 3 AMH, AFC and FSH levels in the control group and in the two endometriosis subgroups [1]p=0.005; [2]p=0.04; [3]p=0.01.

	CONTROL ± SD	ENDOMETRIOSIS-SURGERY SUBGROUP ± SD	ENDOMETRIOSIS-NO SURGERY SUBGROUP ± SD
AMH	3.02 ± 1.22	1.18 ± 0.56[1]	1.67 ± 0.81[2]
AFC	15.20 ± 3.83	9 ± 3.37[3]	10.17 ± 1.94[2]
FSH	8.2 ± 1.8	8.28 ± 3.7	9.78 ± 2.45

AMH: Anti-Müllerian hormone; AFC: Antral follicle count; FSH: Follicle stimulating hormone

Table 4 Fatures of the control group and endometriosis group; [1]p=0.04; [2]p=0.02

	CONTROL GROUP AVERAGE ± SD	ENDOMETRIOSIS GROUP AVERAGE ± SD
Dose of gonadotropin	2010 ± 801.7	2970 ± 878.8 [1]
Cycle stimulation duration	9.7 ± 3.8	9 ± 1.5
Estrogen	1851 ± 973.3	2183 ± 2156
Progesterone	1.16 ± 0.7	1.3 ± 0.9
Number of follicles > 16 mm	6.40 ± 2.30	4.14 ±1.87 [2]
Number of retrived oocytes	6.33 ± 2.58	4.07 ± 1.82 [1]
Number of inseminated oocytes	5.83 ± 2.85	3.79 ± 1.72
Number of fertilized oocytes (2pn)	4.17 ±1.94	2.43 ±1.34
Number of grade I embryos	1.67 ± 1.03	0.42 ± 0.65 2
Number of grade II embryos	0.83 ± 0.75	1.07 ±1.34
Number of grade III embryos	0.0 ± 0.0	0.14 ± 0.36
Total embryos/fertilized oocytes (%)	76.78% ± 25.11	72.62% ± 33.24

in the endometriosis and control group (Figure 1), we noticed that the control group had no grade III (poor quality) embryos, while grade I embryos accounted for more than 66%, versus 26% in the endometriosis group. This result supports the significant difference between the different grades of embryos.

On comparing the control group with the two endometriosis subgroups (surgery and no-surgery), some important differences emerged (Table 5):

- The total dose of gonadotropins was significantly lower in the control group than in the endometriosis-surgery group (2010 ± 801.7 vs 3278 ± 718.9, p=0.04.
- The number of grade I embryos was significantly higher in the control group than in the endometriosis-surgery subgroup (1.67 ± 1.03 vs 0.0 ± 0.0, p=0.003). A significant difference was also found on comparing the control group with the endometriosis-no surgery subgroup (1.67 ± 1.03 vs 1.00 ± 0.63, p=0.05). No differences in the number of grade I embryos were observed between the two endometriosis subgroups.

Discussion

While women with endometriosis-related infertility now have more chance of getting pregnant and having a baby thanks to treatment programs involving the use of ART, the results do not match those observed in other types of infertility. In fact, to date, there is no therapy able to target the ectopic endometrial tissue and remove the cause of the inflammation, oxidative stress and damage to oocytes and reduction of embryo quality. Women affected by endometriosis have:

- poor ovarian reserve. In agreement with the literature [30, 31], the results of our study show a significant difference in levels of both AMH (3.02 ± 1.22 in the control group vs 1.43 ± 0.73 in the endometriosis group, p=0.03) and AFC (15.20 ± 3.83 in the control group vs 9.54 ± 2.76 in the endometriosis group, p=0.03). In particular, analyzing the control group and the two endometriosis subgroups, the difference remains significant, both for AMH and AFC, between the control group and the endometriosis-surgery subgroup (AMH 3.02 ± 1.22 vs 1.18 ± 0.56, p=0.005; AFC 15.20 ± 3.83 vs 9 ± 3.37, p=0.01) and between the control group and the endometriosis-no surgery subgroup (AMH 3.02 ± 1.22 vs 1.67 ± 0.81, p=0.04; AFC 15.20 ± 3.83 vs 10.17 ± 1.94, p=0.04). No significant difference in AMH was found between the two endometriosis subgroups. This could be explained by the type of surgeries used in "endometriotic" women because the surgery should be aimed at preserving fertility in what Lessey *et al*. have defined a sort of "fertility battle" [32]. The presence of a poor ovarian reserve *ab initio* could justify the higher dose of gonadotropin used in women with endometriosis (2010 ± 801.7 UI in the control group vs 2970 ± 878.8 UI in the endometriosis group).
- Poor embryo quality. According to the Istanbul consensus workshop [33] grade I corresponds to embryos of good quality and grade III corresponds to embryos of poor quality. Our study agrees with other studies in the literature [34-36] showing the presence, in "endometriotic" women, of few grade I embryos (66% in the control group vs 26% in the endometriosis group) and more grade III embryos (0% in the control group vs 9% in endometriosis group).
- Poor oocyte quality. To support our results and the idea that the inflamed microenvironment in "endometriotic" women could influence their fertility, we searched the literature for studies about endometriosis/oocyte quality in women with endometriosis. We found many sources dealing with the relationship between inflammation, oxidative stress and poor oocyte quality. In particular, the study by De Broi *et al*. [28] seems to be one of the most complete studies on systemic and local inflammation (corresponding respectively to the analyses of ROS in serum and in follicular fluid). Other studies show how "endometriotic" women have more abnormalities of embryo implantation and an increased abortion rate [37, 38].

Only considering these factors is it possible to understand why "endometriotic" women have such difficulty getting pregnant and having a baby.

Figure 1 Percentages of grade I, II and III embryos in the control group and in the endometriosis group.

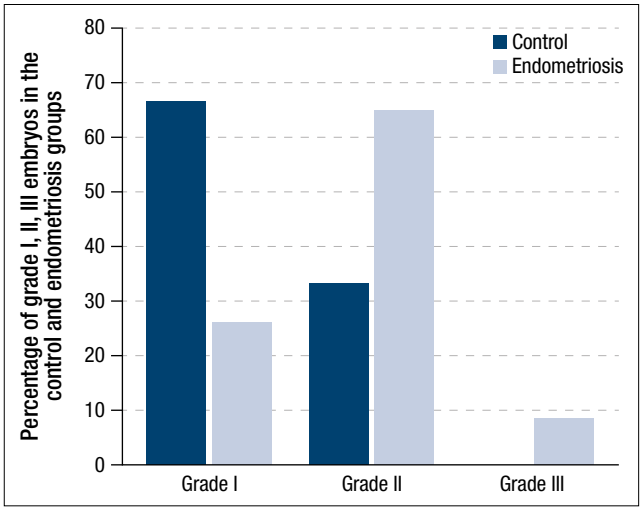

Table 5 Comparison between the control group and the two endometriosis subgroups; p^1=0.04; p^2=0.003; p^3=0.05.

	CONTROL GROUP AVERAGE ± SD	ENDOMETRIOSIS-SURGERY SUBGROUP ± SD	ENDOMETRIOSIS-NO SURGERY SUBGROUP ± SD
Dose of gonadotropin	2010 ± 801.7	3278 ± 718.9 1	2558 ± 963.9
Cycle stimulation duration	9.7 ± 3.8	9.5 ± 1.5	8.3 ± 1.4
Number of grade I embryos	1.67 ± 1.03	0.0 ± 0.0 2	1.00 ±0.63 3
Number of grade II embryos	0.83 ± 0.75	1.50 ± 1.60	0.5 ± 0.84
Number of grade III embryos	0.0 ± 0.0	0.25 ± 0.46	0.0 ± 0.0
Total embryos /fertilized oocytes (%)	76.78% ± 25.11	73.96 ± 23.33	90 ± 22.36

Conclusions

Endometriosis can negatively affect a woman's quality of life because of chronic pelvic pain and subfertility/infertility. A potential factor of infertility is the considerable inflammation that characterizes and influences reproductive function in these women. In the "tubal" women (control group) there is a mechanical problem (closed fallopian tube) that, with ART, can be overcome; in "endometriotic" women the problem is the ectopic endometrium, which causes superinflammation.

Pending further studies that will clarify the pathogenetic mechanisms of endometriosis, we can affirm that inflammation is one of the factors that most compromises oocyte and embryo quality. Better clarifying these mechanisms could improve therapeutic strategies and maximize ART outcomes in patients with endometriosis.

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Declaration of Interest: *The authors declare that there is no conflict of interest*