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Effect of early endometriosis on ovarian reserve and reproductive outcome

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Pelvic Environment in Early Endometriosis
4. Optimal Tests for Measuring Ovarian Reserve
5. Effect of Early Endometriosis on Ovarian Reserve
6. Effect of Early Endometriosis on Luteal Function
7. Effect of Early Endometriosis on Reproductive Outcome in Intrauterine Insemination Treatment
8. Effect of Early Endometriosis on Reproductive Outcome in In vitro Fertilization-Embryo Transfer Treatment
9. Effect of Laparoscopic Resection of Early Endometriosis Lesions on Reproductive Outcome
10. Future Perspective
11. References

1. ABSTRACT

Accumulating evidence suggests that advanced (moderate/severe) endometriosis negatively affects female fecundity, whereas the influence of early (minimal/mild) endometriosis on human reproduction remains unclear. Recent studies showed that the presence of the early pelvic endometriosis lesions deteriorates the ovarian reserve, luteal function, and fertilization rate in infertile women undergoing *in vitro* fertilization-embryo transfer treatment, but not their final reproductive outcome. Meanwhile, laparoscopic resection of early endometriosis lesions may be a promising therapeutic option to improve the fecundity of the affected subfertile women. Insufficient evidence on the relationship between early endometriosis, ovarian reserve, and reproductive outcome warrants further investigations.

2. INTRODUCTION

Endometriosis is recognized as the ectopic presence of the tissues that morphologically resembles endometrium outside the uterine cavity. According to the spread and depth of the ectopic endometriotic implants, the disease has been surgically classified into four stages; minimal (stage I, 1–5 points), mild (stage II, 6–15 points), moderate (stage III, 16–40 points), and severe (stage IV, more than 40 points) (1). Endometriosis is thought to be associated with infertility, as it is found in ~5% of fertile women and ~55% of infertile women (2). There is a growing body of evidence that advanced (moderate/severe) endometriosis reduces female fecundity via multiple mechanisms including impairment of folliculogenesis and oocyte quality in the ovaries, exposure of oocytes to an unfavorable immunologic microenvironment in the peritoneal cavity, impediment of oocyte pickup and transportation in the Fallopian tubes, and defect in embryo receptivity in the eutopic endometrium. By contrast, the impact of early (minimal/mild) endometriosis on human reproduction remains largely undetermined. The aim of this article was to update the information on the ovarian reserve and reproductive outcome in infertile women with early endometriosis.

3. PELVIC ENVIRONMRNT IN EARLY ENDOMETRIOSIS

Unusual network of pelvic humoral and cellular immune factors has been shown to modulate the growth and expansion of the ectopic endometriotic implants in endometriosis. For example, infertile women with endometriosis produce larger volume of peritoneal fluid with higher concentration of activated macrophages, chemokines, cytokines, prostaglandins, and proteases compared with infertile women without endometriosis. It is conceivable that these uncommon local immunological conditions potentially aggravate the function of the genital organs as well as the quality of the gametes and embryos.

Interestingly, a wider variety of chemokines, cytokines, and growth factors (e.g., interleukin-6 and tumor necrosis factor-alpha) are found in the peritoneal fluid with the early endometriosis lesions than in those with the advanced endometriosis lesions (3, 4). Furthermore, there is a significant inverse correlation between the peritoneal macrophage counts/cytotoxicity and the stage of endometriosis (5, 6). These findings support the idea that the local inflammatory responses are more intense in the early endometriosis lesions rather than in the advanced endometriosis lesions.

Table 1. Effect of early endometriosis on ovarian reserve

Parameter	Subject group (Early endometriosis proven by laparoscopy, n=17)	Control group (Tubal occlusion without endometriosis proven by laparoscopy, n=17)	*P* value
Age (years, median and range)	29.5 (20–37)	30.5 (24–37)	>0.05
Body mass index (kg/m^2, mean SD)	22.2 +/- 2.0	22.0 +/- 2.4	0.472
Day 3 serum FSH (IU/mL, mean SD)	5.2 +/- 1.8	4.9 +/- 1.0	>0.05
Day 3 AFC (mean SD)	12.0 +/- 1.3	11.0 +/- 1.6	0.732
Day 3 serum AMH (ng/mL, mean SD)	1.26 +/- 0.70	2.02 +/- 0.72	0.004
Source: Reproduced with permission from (13). Serum AMH concentration on day 3 in the menstrual cycle, but not AFC or FSH concentration, was significantly lower in infertile patients with early endometriosis compared with those with tubal occlusion but without endometriosis			

Studies point out the involvement of the altered uterine contractility during the menstrual period in the pathogenesis and etiology of early endometriosis. In women with mild endometriosis, basal intrauterine pressure, frequency and amplitude of myometrial contraction, and episode of retrograde intraperitoneal menstrual efflux were much higher than in those without endometriosis (7).

4. OPTIMAL TESTS FOR MEASURING OVARIAN RESERVE

Ovarian reserve represents the number and quality of the oocytes pooled in the ovaries. A large number of ovarian reserve tests have been introduced into clinical practice, but their accuracy and predictability remain controversial (8). In 2010, the European Society of Human Reproduction and Embryology Campus Workshop organized in Bologna reached a consensus on the optimal ovarian reserve tests for poor responders to controlled ovarian stimulation in an *in vitro* fertilization-embryo transfer (IVF-ET) program (9). In these Bologna criteria, antral follicular count (AFC) and serum anti-Mullerian hormone (AMH) measurement were adopted as the most currently reliable ovarian reserve tests.

Human ovarian follicles that are growing beyond 200-400 micrometers in diameter are characterized by granulosa cell organization, follicular antrum formation, and follicular fluid accumulation. The follicular development and expansion at this stage are supported by osmotic gradient generated by glycosamonoglycans and proteoglycans, such as hyaluronan, chondroitin sulfate proteoglycan versican, and inter-alpha-trypsin inhibitor in the follicular fluid (10). Antral follicles are visualized on transvaginal ultrasonography as a round-shape hypoechoic area with a diameter of 2 to 10 mm in the human ovaries. AFC represents the total number of the antral follicles in the early follicular phase. AFC has a positive correlation with the size of the primordial follicular pools in the ovaries and the number of oocytes retrieved following controlled ovarian stimulation. Previous studies propose the optimal number of AFC as 5-7 or more, although it remains yet inconclusive (9).

AMH is a soluble 140 kDa dimeric glycoprotein in the transforming growth factor-beta superfamily that is released into blood circulation. AMH is produced by granulosa cells in small growing follicles (including antral follicles), but not in primordial follicles. Thus, serum AMH concentration is thought to reflect the number of the recruited follicles rather than the number of the resting follicles. Mice lacking AMH exhibit accelerated depletion of primordial follicular pools and marked increase in small growing follicle number even under low serum follicle stimulating hormone (FSH) concentration (11). These findings indicate that AMH is a cardinal inhibitor of early recruitment from primordial follicular pools and a potential rate- limiting regulator of FSH sensitivity in the growing follicles. The optimal cut-off values for serum AMH concentration in women of reproductive ages were reported to be in the range between 0.5. and 1.1. ng/ml (9).

One of the current problems in reproductive medicine is that these ovarian reserve tests display a false positive rate of 10–20% and limited predictive property even though the best cut-off values are set. Experts thereby agree that ovarian response in the first IVF cycle may be utilized as a substitute ovarian reserve test (12).

5. EFFECT OF EARLY ENDOMETRIOSIS ON OVARIAN RESERVE

Using AFC and AMH measurement, Lemos et al. (13) prospectively compared the ovarian reserve on day 3 in the natural menstrual cycle between infertile patients with early endometriosis versus those with tubal occlusion but without endometriosis. While AFC on ultrasound and serum basal FSH concentration were similar between two groups, serum AMH concentration was significantly lower in patients with early endometriosis than in those with tubal occlusion only (Table 1). Early endometriosis therefore seems to be associated with a decrease in ovarian reserve. In addition, they reported that the diameter of the selectable follicles, which are the antral follicles that exhibit FSH-dependent growth, was more heterogeneous (p value < 0.0.01 by Levene's test for standard deviation comparison) in the early endometriosis group compared with the tubal occlusion group, although its clinical significances remain unknown.

Table 2. Summary of systematic reviews analyzing the effect of the medical intervention for infertile/ subfertile women with minimal/mild endometriosis on reproductive outcome

Reference citation number	Subject group	Control group	Implantation rate	Clinical pregnancy rate	Live birth rate
22	IVF-ET for infertile patients with early endometriosis proven by laparoscopy	IVF-ET for infertile patients without any endometriosis proven by laparoscopy	Relative risk 0.83, 95% confidence interval 0.68-1.01, p value 0.07	Relative risk 0.94, 95% confidence interval 0.83-1.07, p value 0.35	Relative risk 0.92, 95% confidence interval 0.83-1.02, p value 0.10
26	Surgical laparoscopy for subfertile women with early endometriosis	Diagnostic laparoscopy for subfertile women with early endometriosis	-	Odds ratio 1.89, 95% confidence interval 1.25-2.86, p value 0.003	Odds ratio 1.94, 95% confidence interval 1.20-3.16, p value 0.007
IVT-ET: *in vitro* fertilization-embryo transfer					

Meanwhile, Da Broi et al. (14) explored the effect of the follicular fluid aspirated from infertile women with mild endometriosis during oocyte pickup in IVF cycles on immature bovine oocytes undergoing *in vitro* maturation. The rate of the meiotically-normal oocytes acquired in cultivation was significantly lower in the presence of the follicular fluid from the mild endometriosis cases compared with the control culture (in the follicular fluid without endometriosis or the absence of follicular fluid addition). The findings implicate that the mild endometriosis lesions exacerbate the oocyte quality of the affected women by compromising nuclear maturation and meiotic spindle formation. Moreover, peritoneal fluid obtained from women with endometriosis has been shown to induce microtubule and chromosomal anomalies, and apoptotic degeneration in the mouse oocytes, which were prevented by administration of anti-oxidant L-carnitine. Oxidative stress is therefore likely to be a potential factor that impairs oocyte meiosis in early endometriosis (15).

6. EFFECT OF EARLY ENDOMETRIOSIS ON LUTEAL FUNCTION

Literature points out luteal dysfunction in infertile women with early endometriosis as well as advanced endometriosis. Cunha-Filho *et al*. (16) showed that infertile patients with early endometriosis have significantly lower serum estradiol and progesterone concentration in the late luteal phase than those without endometriosis. Vuorento *et al*. (17) reported unstable daily salivary progesterone secretion patterns in infertile patients with mild endometriosis. Additionally, the normal menstrual cycles were significantly less frequent in patients than in control women.

7. EFFECT OF EARLY ENDOMETRIOSIS ON REPRODUCTIVE OUTCOME IN INTRAUTERINE INSEMINATION TREATMENT

The effect of early endometriosis on reproductive outcome following non-IVF-ET infertility treatment remains controversial. Some earlier studies demonstrated a significantly lower clinical pregnancy rate in intrauterine insemination in infertile women with early endometriosis than in those with unexplained etiology (18, 19). By contrast, others reported that both clinical pregnancy rate per cycle and cumulative live birth rate following controlled ovarian stimulation and intrauterine insemination treatment were similar between infertile women with surgically treated early endometriosis and those with unexplained etiology (20).

8. EFFECT OF EARLY ENDOMETRIOSIS ON REPRODUCTIVE OUTCOME IN *IN VITRO* FERTILIZATION – EMBRYO TRANSFER TREATMENT

In 2002, meta-analysis demonstrated that infertile women with early endometriosis had a significantly lower implantation rate (odds ratio 0.88, 95% confidence interval 0.85–0.90) in IVF-ET treatment, but not the clinical pregnancy rate (odds ratio 0.79, 95% confidence interval 0.60–1.03), than infertile women with tubal factor. However, this analysis failed to separate the studies that endometriosis was pharmacologically and/or surgically treated prior to the initiation of IVF-ET from the studies without previous intervention for endometriosis (21).

This bias is removed by more recent systematic review (22), which concluded that the presence of early endometriosis did not affect any of the implantation rate (relative risk 0.83, 95% confidential interval 0.68–1.01, and p value 0.07), clinical pregnancy rate (relative risk 0.94, 95% confidential interval 0.83–1.07, and p value 0.35), or live birth rate (relative risk 0.92, 95% confidential interval 0.83–1.02, and p value 0.1) in IVF-ET treatment (Table 2). Meanwhile, these authors confirmed that the presence of advanced endometriosis significantly reduces the implantation rate (relative risk 0.79, 95% confidence interval 0.67-0.93, p value 0.006) and clinical pregnancy rate (relative risk 0.79, 95% confidence interval 0.69-0.91, p value 0.0008), but not live birth rate, in the affected infertile women compared with infertile women

without endometriosis (22). These results indicate that, in contrast to advanced endometriosis, early endometriosis is unlikely to affect any indices of reproductive outcome in infertile women undergoing IVF-ET (23).

Intriguingly, both studies (21, 22) disclosed that, compared with infertile women without endometriosis, the fertilization rate in IVF procedure was significantly lower in infertile patients with early endometriosis, but not in those with advanced endometriosis (odds ratio 0.94, 95% confidence interval 0.93–0.96 in ref 21; relative risk 0.93, 95% confidence interval 0.87–0.99, p value 0.03 in reference 22). This paradoxical finding may result from deterioration of oocyte quality or defective insemination ability in the active pelvic inflammatory environment in early endometriosis, but the caution should be exercised for data interpretation to confirm the results.

9. EFFECT OF LAPAROSCOPIC RESECTION OF EARLY ENDOMETRIOSIS LESIONS ON REPRODUCTIVE OUTCOME

Several randomized controlled studies investigated if surgical treatment for early endometriosis improves fecundity in the affected subfertile women. In 1997, Canadian multicenter trial (ENDOCAN study) (24) showed that laparoscopic resection, ablation, and adhesiolysis of visible early endometriosis lesions increases cumulative ongoing pregnancy rate in these affected subfertile women compared with diagnostic laparoscopic only. On the contrary, the Italian study group (GISE) did not find the benefits of these surgical treatments to enhance the fecundity of infertile patients with early endometriosis (25). Recent meta- analysis of these randomized controlled trials support an advantage of laparoscopic surgery to increase the clinical pregnancy rate (odds ratio 1.89, 95% confidential interval 1.25-2.86, p value 0.003) and live birth/ongoing pregnancy rate (odds ratio 1.94, 95% confidential interval 1.20-3.16, p value 0.007) over diagnostic laparoscopy (Table 2) (26, 27). The authors, however, gave a caution about the conflicting results of these two studies.

10. FUTURE PERSPECTIVE

The studies so far suggest a negative impact of early endometriosis on ovarian reserve along with luteal function, but not on reproductive outcome in infertile women undergoing IVF-ET treatment. Laparoscopic resection of early endometriosis lesions is yet a promising therapeutic option to improve the fecundity of the affected subfertile women. Sufficient evidence is lacking to draw conclusions on the relationship between early endometriosis and ovarian reserve in infertile women. Recent reports pointed out the presence of the “occult” endometriosis lesions in the apparently normal peritoneum (28). The findings warrant further investigations if such ultra-early stage lesions relates to early endometriosis and affect the ovarian reserve and reproductive outcome in women desiring babies.

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Abbreviations: IVF-ET: *in vitro* fertilization-embryo transfer, AFC: antral follicular count, AMH: anti-Mullerian hormone, FSH: follicle stimulating hormone

Key Words: Anti-Mullerian hormone, Antral follicular count, Early endometriosis, Ovarian reserve, Reproductive outcome, Review

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