Commentary

Women's **Health**

The impact of endometriosis on fertility

"Although the prevalence of endometriosis in infertile women seemed to be nearly 50%, all women with endometriosis are not infertile..."

Background

Endometriosis, an enigmatic progressive and estrogen-dependent disease characterized by development of endometrial tissue outside of the uterus, causes pain and infertility on reproductive-aged women [1–4]. The health-related quality of the afflicted women's life is seriously decreased due to chronic pelvic pain and subfertility. Endometriosis was first described by Sampson in 1921 [5]. Although the exact prevalence of endometriosis is not well known, it was speculated as 10% of reproductive-aged women. However, a recent epidemiologic study has shown that the prevalence of endometriosis is 1.5% [6]. The prevalence of endometriosis asymptomatic parous women who underwent laparoscopy due to tubal ligation or other benign pelvic pathology had been reached to approximately 40% [7]. However, the prevalence of endometriosis in infertile women has been reported as 9–50% [2–4]. This severity of disease increases by older age due to progression of endometriosis. The advanced stages of endometriosis lead to the lesser fecundity.

Although the prevalence of endometriosis in infertile women seemed to be nearly 50%, all women with endometriosis are not infertile actually. Women diagnosed to have endometrioma by ultrasonography may still achieve a spontaneous pregnancy. Hence, endometriosis is not a direct cause of infertility. Monthly fecundity rates drop from 25% to 2–10% in endometriosis [8]. Endometriosis has associations with infertility; however, the exact mechanisms are yet to be defined and scientific evidence has not completely established.

The poor pregnancy outcomes in endometriosis patients were linked to reduced ovarian reserve, low numbers of oocytes retrieved, lower oocyte and embryo quality, impairment of implantation associated with reduced endometrial receptivity, especially in severe endometriosis, although contradicting reports suggest similar results with control cases.

Live birth rates in women with endometriosis are comparable to women with other causes in the SART reports [9]. Additionally, adverse pregnancy outcomes, such as pregnancy loss, preterm delivery, pre-eclampsia and intrauterine growth restriction, have been demonstrated to occur more frequently in subjects with endometriosis [10,11].

Mechanisms of infertility in endometriosis

The associations of infertility and endometriosis can be assessed by four sections:

- Chronic inflammation;

- Tuboperitoneal distortion;

- Hormonal changes on implantation;

- Decrease in ovarian reserve.

Chronic inflammation

Endometriosis is a chronic inflammatory state [12–14]. Normally, refluxed endome-

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trial tissue is cleared from the peritoneum by the immune system, and the dysregulation of this clearance mechanism has been implicated in the predisposition to implantation and growth of endometrial cells. Interestingly, larger tissue fragments as opposed to individual cells demonstrate an increased capacity to implant, presumably owing to the protection from immune clearance afforded the cells residing on the inner aspects of such fragments. Women with endometriosis have been shown to have an increased volume of peritoneal fluid, as well as increased peritoneal fluid concentrations of prostaglandins, proteases and cytokines including inflammatory cytokines such as IL-1, IL-6, MCP-1 and TNF-α, and angiogenic cytokines, such as IL-8 and VEGF produced by macrophages as shown by our group and the others [15–21]. Peritoneal fluid from women with endometriosis contains more macrophages and activated macrophages, which was initially considered a consequence of low-grade inflammation. More recently, it was recognized that women with endometriosis have higher chemotactic activity for macrophages in their peritoneal fluid [22] and that medical treatment of endometriosis can reduce this [23].

> "Patients with endometriosis have reduced number of preovulatory follicles, follicular growth, dominant follicle size and follicular estradiol concentrations in their ovaries."

The increase in inflammatory cytokines affects oocyte, sperm transport and implantation process. Additionally, the eutopic endometrium from women with endometriosis was found to be more resistant to lysis by natural killer (NK) cells than the eutopic endometrium from women without disease [22]. Subsequent studies identified the constitutive shedding of intercellular adhesion molecule-1 by endometrial stromal cells from women with endometriosis as the potential mechanism by which these cells escape NK cell-mediated clearance [24,25]. Impaired NK cell function may confer an immune-privileged status on the refluxed endometrial cells, thereby predisposing to disease. Menstrual effluent has a harmful effect on the mesothelium and may autologously induce the local injury that promotes the implantation of endometrial cells [13]. Gene expression profiling of the peritoneum from subjects with and without endometriosis demonstrated upregulation of matrix metalloproteinase (MMP)-3 during the luteal phase and upregulation of intercellular adhesion molecule-1, TGF-β and IL-6 during the menstrual phase [13,26]. We have shown that doxycycline decreased the MMP immunostaining in the endometrial implants and the size of the implants, demonstrating that MMPs are playing active role in the development of endometriosis [27]. These increased

inflammatory cytokines increase phagocytotic responses of activated macrophages, which can give harm to oocyte and sperm.

Women with endometriosis have increased endometrial mRNA levels of α_V integrin, combined $\alpha_V\beta_3$ integrins and increased peritoneal IL-1β mRNA levels but decreased peritoneal MCP-1 mRNA levels in menstrual phase of their cycles compared with control subjects. They have increased endometrial mRNA levels of IL-1β and RANTES [18–24] and higher endometrial aromatase mRNA expression in combined phases. Peritoneal mRNA expression of RANTES and VCAM-1 was reported to increase in women with endometriosis during the menstrual phase compared with luteal phase [28–30]. The evidence from increased expression of aromatase, cytokines and adhesion factors in endometrium and peritoneum suggests that both tissues are involved in the pathogenesis of endometriosis.

Minimal/mild endometriosis is associated with increased production of prostaglandins, metalloproteinases, cytokines and chemokines leading to inflammatory process [12]. It is still unknown if inflammation predisposes to, or results from, endometriosis. These alterations may have adverse effects on oocyte, sperm, embryo, or fallopian tube function impairs ovarian, peritoneal, tubal, and endometrial function, leading to defective folliculogenesis, fertilization and/or implantation [31].

There are recently discovered chemokines involved in endometriosis; ENA-78 [32] and SDF-1 [33]. These both cytokines are related Il-8, inducing inflammation and angiogenesis. Furthermore, this chronic state impairs fertilization and implantation via loss of implantation markers.

Tuboperitoneal anatomic distortion

Endometriosis leads adhesions around fallopian tubes, ovary and Douglas pouch. These adhesions can be found as filmy or dense which can be only diagnosed by laparoscopy or laparotomy. These adhesions can block tubal motility and/or impair the oocyte-pickup function of fimbrial end. Especially, ovary having endometrioma is densely adhered to fossa ovarica frequently which can have a detrimental effect on oocyte pickup.

Adhesions on tuboovarian junction can decrease tubal motility. These adhesions would be found on tubal end which can cause distal tubal disease. Distal tubal pathologies that are mainly fimosis could be diagnosed easily by hysterosalpingography. Progression of distal tubal diseases may lead to total functional loss that is hydrosalpenx. The villus in swollen tube would lose its motility which can further impair oocyte transport. However, the impairment of the oocyte-pickup function of fimbrial end may be due to distal tubal obstruc-

tion. These functional disorders that would be revealed by laparoscopy can be accused by endometriosis.

Hormonal changes on implantation

NK cell activity and IgG and IgA antibodies and lymphocytes may be increased in the endometrium of women with endometriosis [34]. These abnormalities may alter endometrial receptivity and embryo implantation. Autoantibodies to endometrial antigens are reported to be increased in some women with endometriosis [35].

The impaired luteinizing hormone (LH) production as the primary pathophysiology causing impaired ovulation [36]. Endometriosis is associated with the luteinized unruptured follicle syndrome and with a sterile low-grade inflammatory reaction in the peritoneal cavity as judged by an increased amount of activated macrophages and their secretion products [37]. In healthy women, the steroid hormone concentrations in peritoneal fluid are much higher after ovulation, but this is not observed in women with the luteinized unruptured follicle syndrome.

Gonadotropin-surge attenuating factor (GnSAF) primarily produced by small follicles leads to a decrease in LH levels in endometriosis patients. GnSAF also decreases the ability of E2 to sensitize the pituitary to gonadotropin-releasing hormone for the positive feedback before LH surge leading suboptimal LH levels and impaired ovulation [38].

Increased levels of IL-6 in the preovulatory follicles of endometriosis patients cause aromatase activity to decrease through the MAPK signal pathway. This leads to a decrease in intrafollicular conversion of androstenedione to estrone and a diminished conversion of androstenedione to testosterone, which is aromatized to E2 [39]. In the final, decreased follicular levels of E2 may result in decreased fertilizing capacity [39].

There is a well-known progesterone resistance in endometriosis [40,41]. This resistance could change implantation window period, which would further cause loss of implantation markers. The inadequacy of pinopodes and other markers yield to defective implantation process, which can lead to infertility. On the other hand, in patients with endometriosis there is well-documented increased aromatase enzyme activity in endometrium, which may further impair implantation. The concomitancy of progesterone resistance and increased aromatase activity affect the implantation throughout 5–6 days of implantation window period.

Decrease on ovarian reserve

Ovarian endometriosis which is endometrioma decreases ovarian reserve itself in especially bilateral involvement [42]. The decrease on reserve would affect oocyte/embryo quality that could lead to decrease pregnancy rates in spontaneous gestation and IVF/ICSI cycles. Patients with endometriosis have reduced number of preovulatory follicles, follicular growth, dominant follicle size and follicular estradiol concentrations in their ovaries [43–45]. These patients have altered hormone profiles, in other words, reduced estrogen, androgen and progesterone and increased activin in their follicular fluid [46].

Decreased AMH levels after surgical excision of endometriomas suggest a surgery-related damage to ovarian reserve [47,48]. Furthermore, even unilateral endometrioma excisional surgery is associated with a significant reduction in ovarian reserve. The reduction is immediate and sustained over time. AMH appears to be a better indicator for postoperative quantification of the ovarian reserve [49]. However, Esinler *et al.* have demonstrated that endometriomas ≤3 cm in diameter *per se* did not have a deleterious effect on ovarian reserve in ICSI cycles [50].

Endometrial polyps

Endometrial polyps are estrogen dependent like endometriosis and estrogen receptors and aromataselevels are shown to be increased in polyps [51] and polyp removal increasespregnancy rate in women with unexplained infertility [52]. A recent meta-analysis showed that endometrial polyps are increased in woment with endometriosis (relative risk: 2.8 [95% CI: 2.48–3.18]) [53].

Conclusion

In conclusion, endometriosis is a disease where infertility may be seen. The reasons for infertility may be due to cytokine release due to inflammatory process of endometriosis, tuboperitoneal anatomic distortion, decrease in implantations, decreased ovarian reserve and endometrial polyps. The gynecologist must inform the patient about these mechanisms, and refer

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Executive summary

- The advanced stages of endometriosis lead to the lesser fecundity.
- Endometriosis is not a direct cause of infertility.
- Monthly fecundity rates drop from 25% to 2–10% in endometriosis.
- Mechanisms of infertility in endometriosis involve chronic inflammation, tuboperitoneal distortion, hormonal changes on implantation, decrease in ovarian reserve and endometrial polyps.

the patient to an infertility specialist to discuss her future fertility potential.

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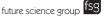The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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