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Short Communication

Stages of endometriosis: Does it affect *in vitro* fertilization outcome

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ABSTRACT

Objective: Women with endometriosis often need *in vitro* fertilization (IVF) to conceive. There are conflicting data on the results of IVF in patients with endometriosis. The present study was undertaken to investigate whether or not the stage of endometriosis affects the IVF outcome in order to give the best patient counseling

Materials and methods: We compared IVF outcome measures between 40 patients with surgically confirmed minimal and mild endometriosis (American Society for Reproductive Medicine Stage I/II) and 38 patients with moderate and severe endometriosis (Stage III/IV). Each group was also compared with a control group of 157 patients with tubal factor infertility. Outcome measures included number of follicles, number of oocytes, mean number of ampoules of gonadotropins, cumulative pregnancy, and live birth rates

Results: Higher cancelation rates, higher total gonadotropin requirements, and lower oocyte yield were found in women with endometriosis Stage III and IV compared with both the Stage I/II and control groups. The fertilization rate was higher in Stage III/IV endometriosis compared to Stage I/II. Clinical pregnancy and live birth rates were comparable between patients with endometriosis Stage I/II and control group, whereas they were significantly lower in patients with endometriosis Stage III/IV compared to other two groups.

Conclusion: The American Society for Reproductive Medicine classification of endometriosis is useful in predicting IVF outcome. Advanced endometriosis means a worse prognosis for IVF treatment compared to milder stages or tubal factor infertility. The decreased fertilization rate in Stage I/II endometriosis might be a cause of subfertility in these women, as a result of a hostile environment caused by the disease.

Introduction

Endometriosis is one of the most puzzling gynecologic diseases. It affects 2–10% of women in general population and 20–50% of women who are investigated for infertility [1]. This high prevalence of endometriosis in infertile women has led to the assumption that there might be a causal relation between endometriosis and infertility. Despite extensive studies, the exact mechanism by which endometriosis causes infertility is not clearly understood. According to European Society of Human Reproduction and Embryology guidelines, *in vitro* fertilization and embryo transfer (IVF-ET) is an appropriate treatment in cases of infertility with a history of endometriosis. Using IVF-ET, it is possible to bypass the suspected disturbed functions that are affected in natural cycles by endometriosis, such as altered folliculogenesis, ovulatory dysfunction, oocyte maturation, cleavage of embryo, and implantation [2,3].

Whether the results of IVF-ET are as good in women with endometriosis as in patients with other causes of infertility is a matter for discussion. The results of different studies are controversial. Some investigators have reported poor IVF outcome in women with endometriosis-related infertility [4,5], whereas others reported high success rates comparable to those in women with tubal factor infertility [6,7]. Furthermore, some studies reported that women with advanced stage endometriosis and previous surgery responded less well to gonadotropin stimulation and had lower fertilization rates but the effect of different stages of endometriosis on IVF-ET outcome remains unclear [8].

The present study was undertaken to investigate whether or not the stage of endometriosis affects the IVF outcome in order to give the best patient counseling.

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Table 1
Patient characteristics and controlled ovarian hyperstimulation parameters. Data are expressed as mean ± standard deviation where appropriate.

	Endometriosis I/II (A)	Endometriosis III/IV (B)	Tubal factor (C)	A vs. C	B vs. C	A vs. B
No. of patients	40	38	157			
Age, y	34.7 ± 4.3	30.8 ± 4.8	33.2 ± 3.2	NS	<0.01	<0.01
BMI, kg/m^2	25.4 ± 5.2	24.7 ± 4.7	25.7 ± 6.1	NS	NS	NS
Duration of infertility, y	8.1 ± 3.7	5.8 ± 2.4	7.7 ± 4.3	NS	<0.05	<0.05
Basal serum FSH, IU/mL	7 ± 2.9	6.1 ± 2.8	7.6 ± 2.9	NS	<0.05	NS
Mean no. of ampoules of gonadotropin	33.7 ± 11.2	37.5 ± 16.2	27.2 ± 9.5	<0.05	<0.01	NS
Duration of stimulation, d	8.9 ± 2.1	10.5 ± 3.2	9.22 ± 1.8	NS	<0.05	NS
E2 Day 7, pg/mL	722 ± 566	698 ± 423	822 ± 678	<0.05	<0.05	NS
No. of follicles ≥16 mm	6.9 ± 5.2	4.79 ± 4.5	7.9 ± 6.4	<0.01	<0.005	<0.05

BMI = body mass index; E2 = estradiol; FSH = follicle-stimulating hormone; NS = not significant.

Materials and methods

A total of 235 first-attempt IVF cycles performed in two IVF units were prospectively analyzed. Of these, 78 patients were diagnosed with endometriosis, and all had previously undergone laparoscopy. Forty patients were diagnosed with minimal and mild endometriosis [American Society for Reproductive Medicine (ASRM) Stage I/II] and 38 with moderate and severe endometriosis (ASRM Stage III/IV). Sixty-eight patients had undergone only one, and 12 more than one surgical procedure. In all patients with ovarian endometriosis the *stripping* technique was used to excide endometriomas (the endometrioma was drained with aspiration and the pseudocapsule was dissected by gentle traction and countertraction using two 5-mm grasping forceps) and the diagnosis was confirmed histologically. All patients with endometriosis were treated with three to six cycles of gonadotropin-releasing hormone (GnRH) analogues after laparoscopy and prior to IVF. The control group consisted of 157 women who underwent IVF treatment during the same time period, with laparoscopically diagnosed tubal factor infertility and without any evidence of endometriosis. The comparison was made separately between the group of patients with endometriosis Stage I/II and the control group and patients with endometriosis Stage III/IV and the control group. Results were also compared between patients with Stage I/II and Stage III/IV endometriosis.

Depending on the women's age, the antral follicle count and the basal (Day 3) follicle-stimulating hormone (FSH) concentration, the long GnRH-agonist downregulation protocol [triptorelin embonate (Diphereline) 0.1 mg; Ipsen Pharma Biotech, Paris, France], the short GnRH-agonist or GnRH antagonist protocol (Cetrotide; Serono Pharma, Geneva, Switzerland) were used. Ovulation stimulations were conducted with daily subcutaneous injections of individual starting doses of recombinant FSH (Folitropin α-Gonal F; Serono Pharma; or Folitropin β; Puregon; Organon, Oss, The Netherlands) or human menopausal gonadotropin (Menopur, Feriing, Germany) at appropriate doses (50–450 IU). Ovarian response to gonadotropins was monitored by transvaginal ultrasound and serum estradiol (E2) measurement every second day from Day 7. Ovulation was triggered by injecting 10,000 IU human chorionic gonadotropin (hCG) when the leading follicle reached 18 mm with appropriate serum E2 levels. Thirty-six hours after administration of hCG transvaginal ultrasound-guided oocyte aspiration was performed under local anesthesia. After cultivation, ET was performed 3–5 days after oocytes aspiration. All patients received luteal phase support for 2 weeks. Clinical pregnancy was defined as the visualization of gestational sac at ultrasound examination and biochemical pregnancy was defined as detection of β-HCG levels in serum but no signs of pregnancy by ultrasound.

Data are expressed as the mean ± standard deviation or as percentages when required. Statistical comparisons among groups were performed using the Fisher exact test, χ^2 test, Wilcoxon's test, or Student *t* test as appropriate. Significance was defined as a *p* value <0.05.

Results

Patient characteristics and ovarian stimulation parameters are shown in Table 1. Patients with Stage III and IV endometriosis had lower basal serum FSH levels and required longer stimulation compared with the control group, whereas all patients with endometriosis (unrelated to the stage of disease) required more ampoules of gonadotropins, and attained lower serum E2 levels on Day 7 and fewer of follicles ≥16 mm on the day of hCG administration compared with the control group. Moreover, the number of follicles ≥16 mm on the day of hCG administration was significantly lower in patients with Stage III and IV endometriosis compared with those with endometriosis Stage I and II. Finally, patients with endometriosis Stage III and IV were younger and had a shorter duration of infertility compared with other two groups of patients.

IVF laboratory parameters and IVF outcomes are presented in Table 2. Patients with endometriosis Stage III and IV had significantly higher cycle cancellation rates and higher fertilization rates but fewer retrieved oocytes, fewer total number of embryos, and lower implantation rates compared with the other two groups of patients. Clinical pregnancy rates, multifetal pregnancy rates, and live birth rates were comparable between patients with endometriosis Stage I and II and control group, whereas all those parameters were significantly lower in patients with endometriosis Stage III and IV compared with the other two groups of patients.

The body mass index and miscarriage rate showed no significant differences between groups.

Discussion

According to our data, severe endometriosis has a negative influence on IVF outcome. With increasing severity of endometriosis, a poorer success rate for IVF was observed. Almost all aspects of IVF are negatively influenced by moderate and severe endometriosis, from ovarian reserve and ovarian response during gonadotropin stimulation to implantation and pregnancy rate. The only exception was the fertilization rate.

Analyzing the patient characteristics, we can see that patients with advanced stages of endometriosis were younger and had a shorter duration of infertility when beginning IVF. This can simply be explained by the fact that patients with severe endometriosis have other symptoms beside infertility (dysmenorrhea, dyspareunia, chronic pelvic pain) when they visit the gynecologist who refers them to laparoscopy and IVF.

The negative association between advanced endometriosis and ovarian reserve, ovarian response during stimulation and cancellation rate might be ascribed to the effect of previous surgical treatment and to endometriosis as a disease itself. Studies supporting the theory of surgery-mediated damage showed removal of healthy tissue by laparoscopic stripping and surgery related local inflammation or vascular compromise following electrosurgical coagulation [8,9]. By contrast, using pathological sections of the

Table 2
In vitro fertilization laboratory parameters and outcome in women with different stages of endometriosis and women with tubal factor infertility. Data are expressed as mean ± standard deviation when appropriate.

	Endometriosis I/II (A)	Endometriosis III/IV (B)	Tubal factor (C)	A vs. C	B vs. C	A vs. B
Cycle cancellation rate, %	12.7	20.8	5.7	<0.01	<0.005	<0.05
No. of oocytes retrieved	5.9	3.6 ± 3.4	7.6 ± 6.1	<0.01	<0.001	<0.05
Fertilization rate, %	49.5	59.8	54.2	NS	<0.01	NS
Mean no. of embryos	3 ± 1.9	1.9 ± 1.6	4 ± 2.8	<0.05	<0.001	<0.01
Implantation rate, %	25.7	17.6	23.11	NS	<0.05	<0.05
Cumulative pregnancy rate per ET, %	43.2	31.03	46.9	NS	<0.001	<0.05
Miscarriages, %	23.5	23.8	19.8	NS	NS	NS
Multifetal pregnancies, %	41.5	27.5	40	NS	<0.01	<0.01
Live birth rate per ET, %	28.8	20.7	27.5	NS	<0.05	<0.05

ET = embryo transfer.

ovarian cortex surrounding endometriomas, Maneschi et al found reduced follicular numbers and activity antecedent to surgery. Whether ovarian damage precedes or follows surgery remains controversial [10]. Elucidation of this point is of utmost interest since it would strongly impact on the decision of whether to operate on women with advance stages of endometriosis who are selected for IVF.

The fertilization rate in women with severe endometriosis was higher than in those with minimal and mild endometriosis and similar to patients with tubal factor infertility. One possible explanation for this may be that lesions associated with severe endometriosis are burned out lesions, resulting in pelvic adhesions rather than lesions with active endometrial glands. Thus it may be the secretory components of an active lesion that affect oocyte quality and thus fertilization, which is the case in milder endometriosis. This supports results of previous studies showing an increase in chemotactic activity in the peritoneal fluid of women with active endometriosis lesions [11–13].

Patients with advanced stages of endometriosis had lower pregnancy and live birth rate compared to control group and patients with minimal and mild endometriosis. Arici and al showed a 60% pregnancy rate per ET in women with Stage I and II of endometriosis and only 7% in women with endometriosis Stage III and IV [14]. Azem et al and three more studies also presented significantly lower pregnancy and live birth rate in patients with Stage III and IV endometriosis [15–18]. Nevertheless it is important to notice that a 21% live birth rate is still a good percentage and probably is the best chance for patients with advanced endometriosis to conceive, given that according to ASRM their monthly pregnancy rate during natural cycling is <2% [19]. Regarding the fact that patients with advanced endometriosis have lower pregnancy and multifetal rates, it can be concluded that fertilization rates are not impaired. Endometrial receptivity is negatively affected in these patients. More studies are needed to support this theory.

Our data have several clinical implications. First, they suggest that IVF outcome is influenced by different stages of endometriosis through different mechanisms. Moderate and severe endometriosis have detrimental effects on ovarian response during stimulation, cycle cancellation rate and implantation rate. Minimal and mild endometriosis impair the fertilization rate due to the occurrence of lesions with active endometrial glands. The ASRM classification has proved to be useful in predicting the IVF outcome and might be used for planning the procedure and counseling patients.

The ASRM classification of endometriosis is useful in predicting the IVF outcome. Stage III and IV endometriosis means a worse prognosis for IVF treatment compared to milder stages or tubal factor infertility. A decreased fertilization rate in Stage I–II endometriosis might be a cause of subfertility in these women, as a result of a hostile environment caused by the disease.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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