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Impact of endometriosis on in vitro fertilization and embryo transfer cycles in young women: a stage-dependent interference

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Abstract

Objective. Endometriosis is a frequent indication for in vitro fertilization and embryo transfer (IVF-ET). Its influence on IVF-ET cycles remains controversial. We evaluated the impact of the severity of endometriosis on IVF-ET cycles in young women. *Design.* Retrospective cohort study. *Setting.* Academic tertiary referral centre. *Sample and Methods.* In a retrospective cohort analysis, 164 IVF-ET cycles in 148 women with endometriosis-associated infertility were analyzed. Eighty cycles performed during the same period on 72 consecutive women with tubal infertility were considered as controls. All patients were younger than 35 years old. *Main Outcome Measures.* Response to controlled ovarian hyperstimulation (COH), number of oocytes retrieved, fertilization, implantation and pregnancy rate (PR). *Results.* Clinical PR was lower in the group with endometriosis (all stages) in comparison with the tubal factor group. Higher total gonadotropin requirements, lower response to COH and lower oocyte yield were also found in the endometriosis group. Stage-stratified analysis showed a lower fertilization rate in stage I–II (52.6% stage I–II, 70.5% stage III–IV and 71.9% tubal factor). In stage III–IV endometriosis there was a higher cycle cancellation rate, a reduced response to COH and a lower PR compared with both the stage I–II and the tubal infertility groups (PR 9.7, 25 and 26.1%, respectively). *Conclusions.* Stage III–IV was strongly associated with poor IVF outcome. A decreased fertilization rate in stage I–II might be a cause of subfertility in these women, owing to a hostile environment caused by the disease.

Abbreviations: ASRM, American Society for Reproductive Medicine; COH, controlled ovarian hyperstimulation; E_2, estradiol; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; IVF, in vitro fertilization; IVF-ET, in vitro fertilization and embryo transfer; PR, pregnancy rate

Introduction

Endometriosis is a well-known cause of subfertility. The reported prevalence of endometriosis found at laparoscopy in infertile women is 25–35%, whereas the prevalence in the general population is 3–12% (1,2). This high prevalence of endometriosis in infertile women has led to the assumption that there might be a causal relation between endometriosis and infertility.

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, especially when associated with compromised tubal function, male factor and/or other treatment failures (3). In a meta-analysis of 22 studies from 1983 to 1997, Barnhart et al. (4) concluded that, overall, endometriosis significantly reduces all markers of the reproductive process, which results in an IVF pregnancy rate that is

almost one-half that for women who undergo IVF for other indications. However, several limitations must be considered when interpreting these results: the meta-analysis did not include randomized controlled trials; some of the included studies were outdated and did not take into account improvements of the IVF-ET protocols and laboratory performances in the last decade; the outcome reported for each study varied, with some studies reporting absolute pregnancy rates, some reporting clinical pregnancy rates and some live birth rates; and articles could not be categorized as to whether the endometriosis was medically or surgically treated before the initiation of IVF-ET or whether endometriotic lesions were present at the time of the cycle (4).

Analysis of large databases (such as Society for Assisted Reproductive Technology (SART) and Human Fertilisation and Embryology Authority (HFEA)) indicates that there is no difference in IVF-ET outcome for women with infertility-related endometriosis. In a more recent publication, Matalliotakis et al. compared the IVF-ET outcomes of 68 women who previously underwent laparoscopic surgery for advanced stage endometriosis and a control group of 106 women with tubal factor infertility. They reported that women with advanced stage endometriosis and previous surgery responded less well to gonadotropin stimulation, but had similar IVF-ET implantation and delivery rates compared with women with tubal factor infertility (5). Thus, the question of whether endometriosis affects the outcome of IVF-ET cycles has not been resolved. Furthermore, the effect of different stages of endometriosis on IVF-ET outcome remains unclear.

The objective of this study was to evaluate the real effect of endometriosis on the IVF-ET cycle parameters and outcome in a carefully selected homogeneous group of young patients who had been previously subjected to surgical treatment for endometriosis, infertile before surgery for endometriosis without clinical/ultrasonographic sign of recurrences. They were compared with a group of patients with tubal infertility undergoing IVF-ET during the same period. The effects of the different stages of endometriosis were also analysed.

Material and methods

During the period from February 2001 to March 2007, 203 patients with the diagnosis of pelvic endometriosis underwent IVF-ET in the Department of Science for the Woman and Child's Health (study group). Our study group consisted of 148 patients with previous surgery for endometriosis. All were infertile before surgery and did not show any clinical/ultrasonographic signs of recurrence. Endometriosis was stratified according to the severity of disease based on the American Society for Reproductive Medicine (ASRM) revised classification system for endometriosis into stage I–II (minimal/mild) and stage III–IV (moderate/severe). The control group included 72 women selected from patients with tubal infertility who were undergoing IVF-ET in the same period. They did not show any clinical/ultrasonographic signs which raised suspicions of endometriosis.

In both groups, patients aged >35 years, with incomplete clinical data and/or with other causes of infertility (such as abnormal partner's semen analysis according to the World Health Organization criteria, infectious disease or a seriously deformed uterus) were excluded.

Women with endometriosis-related infertility underwent 164 IVF-ET cycles, and patients of the control group 80 IVF-ET cycles. To avoid a bias in the evaluation of the fertilization rate, only IVF-ET cycles without intracytoplasmic sperm injection were considered for analysis.

A 'long-acting down-regulation' drug regime was used. Triptorelin (Decapeptyl® 0.1mg, Ipsen Pharma, Milan, Italy) was injected subcutaneously on day 21 of the cycle. After down-regulation (verified after adequate ovarian suppression at pelvic ultrasonography and circulating estradiol (E_2) values below 35pg/ml), we initiated a daily subcutaneous administration of 225–300IU of FSH (highly purified follicle-stimulating hormone, Metrodin HP®, 75IU, or recombinant FSH, Gonal-F®, 600IU; Serono, Rome, Italy). Doses of gonadotropins were individually decided depending on the patient's age, basal FSH, ovarian volume, ovarian antral follicle count and weight, and adjusted according to ovarian response. Serial ultrasound scans and estradiol evaluations were obtained during ovarian stimulations. When at least two follicles reached a maximal diameter of 17–18mm, 10 000IU of human chorionic gonadotropin (hCG; Gonasi®, 5000IU, two ampoules; Amsa, Rome, Italy) were subcutaneously administered. Oocyte retrieval was 36hours later, using vaginal ultrasonography, and the oocytes were fertilized on the same day.

All oocytes retrieved were scored and inseminated for IVF-ET (only three oocytes after the Assisted Reproduction Law 40/2004), and fertilization was assessed the following day. Two or three days after the oocyte retrieval, the embryo transfer was performed.

The luteal phase was supported with both a daily intramuscular administration of 50mg of natural progesterone in oil (Prontogest®; Amsa) and 600mg/day (Progeffik®, 200mg; Effik, Cinisello Balsamo, Milan, Italy) beginning on the night after ovum collection. Pregnancy was assessed through plasma β-hCG values 14days after oocyte retrieval. For patients with β-hCG >5IU/l of plasma, a transvaginal ultrasound scan was performed two weeks later. Clinical pregnancy was defined as the presence of at least one gestational sac by ultrasound examination with a fetal pole and heart activity.

Our primary end-points were the number of stimulation days, number of FSH ampules, number of oocytes retrieved, number of embryos transferred and clinical pregnancy rate.

Table 1. Characteristics of patients.

	Number of patients	Number of cycles	Age (years; mean±SD)	Primary infertility		Duration of infertility (years; mean±SD)
				n	(Percentage)	
Endometriosis						
All stages	148	164	31.3±2.9	131	(88.5)	3.9±2.6
Stage I–II	54	55	31.8±3.3	45	(83.3)	4.8±2.7
Stage III–IV	94	109	31±2.5	86	(91.5)	3.3±2.4
Tubal factor	72	80	30.7±3.1	27	(37.5)	3.5±2.8

Note: Primary infertility in endometriosis (all stages, I–II and III–IV) vs. tubal factor: p=0.0001.

Secondary end-points included fertilization, implantation and cancellation rates. The study design was approved by our internal committee.

Statistical methods

Data are expressed as means±SD or percentages as required. Statistical analyses were performed using a unpaired t-test for parametric data or a χ^2 test for categorical data. A p-value <0.05 was considered to be significant. All statistical analyses were performed using the Statistical Package for Social Sciences software, version 18 (SPSS Inc., Chicago, IL, USA).

Results

Patients in the two groups were comparable in terms of age and duration of infertility. Most infertile women with endometriosis had primary infertility (88.5% of women with endometriosis vs. 37.5% of the tubal factor group) and were treated earlier than women with tubal factor infertility (mean infertility duration 3.9±2.6 years in endometriosis group and 3.5±2.8 years in control group; Table 1).

The semen characteristics of the study and control groups' male partners are compared in Table 2. The mean (±SD) sperm concentration proved similar. The mean percentage of sperm with progressive motility was also comparable in the study and control groups. The mean percentage of sperm with normal morphological features was 42.4±24.3% in the endometriosis group and 43.3±20.8% in the tubal factor group.

Our initial analysis was to compare the endometriosis group with women with tubal factor. Table 3 shows the overall outcomes of the IVF-ET cycles separately for women with endometriosis and the control group. In spite of a higher FSH dosage, the numbers of follicles on the day of hCG, oocytes retrieved and embryos obtained and transferred were significantly fewer in women with endometriosis compared with those without. No significant differences were found between the groups with regard to the length of the stimulation phase, cycle cancellation rate, peak E_2 levels, fertilization or implantation.

The statistical analysis demonstrated a significant decrease in the chance of achieving a pregnancy for women with endometriosis compared with women undergoing IVF for tubal factor infertility. Nineteen (11.6%) clinical pregnancies per started cycle were observed in women with endometriosis, and 18 (22.5%) in women with tubal factor infertility (p=0.041). The difference was not significant when clinical pregnancy rates per retrieval or per embryo transfer were considered.

To further investigate differential effects of IVF-ET outcome by stage of endometriosis, we separately compared

Table 2. Comparison of semen characteristics between the endometriosis group and the control group.

Semen characteristics	Partners of women with endometriosis	Partners of women with tubal factor	*p*-Value
Ejaculate volume (ml)	3.7 ± 2.2	3.6 ± 1.7	NS
pH	7.7 ± 0.4	7.5 ± 0.3	NS
Sperm count (10^6/ml)	97.4 ± 71.3	92.1 ± 66.5	NS
Total sperm count (10^6 per ejaculate)	143.7 ± 47.7	212 ± 67.3	NS
Motility a (%)*	43.5 ± 27.7	37.8 ± 13.3	NS
Motility b (%)*	12.7 ± 7.5	18.1 ± 3.4	NS
Morphologically normal spermatozoa (%)	42.4 ± 24.3	43.3 ± 20.8	NS

*Sperm motility is graded according to World Health Organization guidelines (WHO, 1999) (6): rapidly progressive (>25 μm s^{-1}) (grade 'a'), slowly progressive (5–25 μm s^{-1}) (grade 'b').

Table 3. Results of analysis comparing endometriosis patients (any stage) with control women.

	Endometriosis	Tubal factor	*p*-Value
Mean days on gonadotropins	11.8±1.9	11.7±1.9	0.779
Total FSH/hMG (IU)	3 842.1±1 692.2	3 301.9±1 421.7	0.016*
Cycle cancellation rate	17 of 164 (10.4%)	3 of 80 (3.7%)	0.129
Peak E_2 levels (pg/ml)	1 296.5±948.1	1 470.6±975.3	0.222
Number of follicles on day of hCG	11.6±6.5	14.6±6.5	0.001*
Number of follicles ≥15mm on day of hCG	3.7±2.7	2.8±2.6	0.011*
Number of of oocytes retrieved	7.8±5.4	10.8±6.1	0.001*
Fertilization rate (%)	65.3	71.9	0.101
Total number of embryos	2.7±3.1	5±4	0.001*
Mean number of transferred embryos	2.3±1.6	3.1±1.6	0.001*
Total number of pregnancies (β-hCG+)	24	22	0.015*
Number of clinical pregnancies	19	18	0.048*
Implantation rate (%)	8.6	10.8	0.477
Clinical pregnancy rate per patient	(19 of 148) 12.8%	(18 of 72) 25%	0.038*
Clinical pregnancy rate per started cycle	(19 of 164) 11.6%	(18 of 80) 22.5%	0.041*
Clinical pregnancy rate per retrieval	(19 of 147) 12.9%	(18 of 77) 23.4%	0.070
Clinical pregnancy rate per embryo transfer	(19 of 126) 15.1%	(18 of 69) 26.1%	0.092

Abbreviations: hMG, human menopausal gonadotropins; FSH, follicle-stimulating hormone; β-hCG, β-subunit of human chorionic gonadotropin, β-hCG+ when >5IU/l.
*P < 0.05.

Table 4. Results of analysis comparing endometriosis patients (stage I–II and III–IV) with control women.

	Endometriosis stage I–II	Endometriosis stage III–IV	Tubal factor	*p*-Value for endometriosis vs. stage I–II tubal factor	*p*-Value for endometriosis vs. stage III–IV tubal factor	*p*-Value for endometriosis vs. stage I–II stage III–IV
Mean days on gonadotropins	11.9±1.4	11.8±2.1	11.7±1.9	0.300	0.872	0.807
Total FSH/hMG (IU)	3 505.8±1 527.6	4 021.5±1 754.4	3 301.9±1 421.7	0.429	0.003*	0.065
Cycle cancellation rate	2 of 55 (3.6%)	15 of 109 (13.8%)	3 of 80 (3.7%)	0.668	0.039*	0.055
Peak E_2 levels (pg/ml)	1 603.3±954.3	1 108.5±899.6	1 470.6±975.3	0.463	0.019*	0.004*
Number of follicles on day of hCG	14.3±5.6	6.5±0.6	14.6±6.5	0.761	0.001*	0.001*
Number of follicles ≥15mm on day of hCG	3.6±3.1	2.4±2.1	3.7±2.7	0.931	0.0001*	0.003*
Number of oocytes retrieved	9.8±5.5	6.7±5	10.8±6.1	0.347	0.001*	0.001
Fertilization rate (%)	52.6	70.5	71.9	0.0001*	0.805	0.003*
Total number of embryos	2.8±2.9	2.6±3.2	5±4	0.001*	0.001*	0.731
Mean number of transferred embryos	2.4±1.6	2.2±1.6	3.1±1.6	0.016*	0.001*	0.419
Total number of pregnancies (β-hCG+)	14 of 54	10 of 94	22 of 72	0.711	0.002*	0.028*
Implantation rate (%)	14.1	5.3	10.8	0.453	0.055	0.010*
Clinical pregnancy rate per patient	(11 of 54) 20.4%	(8 of 94) 8.5%	(18 of 72) 25%	0.691	0.007*	0.069
Clinical pregnancy rate per started cycle	(11 of 55) 20%	(8 of 109) 7.3%	(18 of 80) 22.5%	0.893	0.006*	0.033*
Clinical pregnancy rate per retrieval	(11 of 53) 20.7%	(8 of 94) 8.5%	(18 of 77) 23.4%	0.890	0.013*	0.062
Clinical pregnancy rate per embryo transfer	(11 of 44) 25%	(8 of 82) 9.7%	(18 of 69) 26.1 %	0.927	0.015*	0.044*

Abbreviations: hMG, human menopausal gonadotropins; FSH, follicle-stimulating hormone; β-hCG, β-subunit of human chorionic gonadotropin, β-hCG+ when >5IU/l.
*P < 0.05.

women with stage I–II endometriosis and those with stage III–IV disease with women with tubal factor infertility. The results of both of these comparisons are presented in Table 4. Patients with a confirmed diagnosis of endometriosis stage I–II showed a significantly lower fertilization rate when compared with the control group (52.6 vs. 71.9%, p=0.0001; total number of embryos 2.8±2.9 vs. 5±4, p=0.001; and mean number of transferred embryos 2.4±1.6 vs. 3.1±1.6, p=0.001, respectively). Similar results were observed regarding all the other outcomes.

A comparison of women with severe endometriosis (stage III–IV) with women with tubal infertility

demonstrated a large reduction in the pregnancy rate. Significant differences were also observed in all the other comparisons; only the fertilization rate in stage III–IV endometriosis was comparable to the tubal factor group (70.5 and 71.9%, respectively, p=0.805).

Women with stage III–IV endometriosis were also directly compared with women with stage I–II endometriosis. The results of this analysis are reported in Table 4. Despite a significantly higher fertilization rate, women with moderate to severe endometriosis had a significantly lower pregnancy rate (clinical pregnancy rate per embryo transfer 9.7 vs. 25%, p=0.044). Women with more severe stages of endometriosis, compared to women with minimal/mild endometriosis, also had a lower peak E_2 concentration, fewer follicles on the day of hCG, fewer oocytes at retrieval and a lower implantation rate.

In the stage III–IV endometriosis group the cycle was discontinued because of poor ovarian response in 15 of 109 cycles (13.8%) compared with only three cycles of 80 (3.7%) in the tubal factor group and two of 55 (3.6%) in the minimal/mild endometriosis group.

Discussion

Endometriosis has become a frequent indication for IVF-ET. Whether endometriosis influences the results of IVF-ET remains a controversial issue. A number of studies have examined IVF-ET outcomes in women with endometriosis, with conflicting evidence. In a systematic review, a reduced response to gonadotropins, lower oocyte yield and poor clinical pregnancy rates per cycle have all been described in patients with endometriosis compared with women with tubal infertility (4). Some studies have reported IVF-ET success rates in endometriosis comparable to those in unexplained or tubal factor infertility or improved outcomes with increasing disease stage (7–9).

Our study showed a detrimental relation between advanced stage endometriosis and IVF-ET outcome, with a significant reduction in pregnancy rates (clinical pregnancy rate per embryo transfer: 9.7% for stage III–IV, 25% for stage I–II and 26.1% for tubal factor). Almost all aspects of IVF-ET negatively influenced women previously treated for severe endometriosis, including peak estradiol concentrations, number of follicles on the day of hCG, number of oocytes retrieved and implantation rates.

The negative association between moderate/severe endometriosis and the number of oocytes retrieved might be ascribed to the effect of previous surgical treatment more than to the disease endometriosis itself. Ovarian cystectomy has been associated with damage to healthy ovarian tissue and reduction in ovarian reserve (10,11). Furthermore, in patients with more severe stages, major pelvic adhesions (including those that result from endometriosis) can impair oocyte release from the ovary or inhibit ovum pick-up or transport (12,13). Our data support the defective implantation in stage III–IV previously described. Lack of understanding with regard to the mechanisms of embryo implantation makes it difficult to explain why women with endometriosis may have a decreased implantation capacity (14). Reduced endometrial receptivity might be secondary to delayed histological maturation or biochemical disorders, reduction of $\alpha v\beta 3$ integrin expression or dysregulation of other select genes in the endometrium (14).

Aboulghar et al. reported that the outcome of IVF-ET in stage IV endometriosis with previous surgery was significantly lower with a cycle cancellation in 29.7% of the study group compared with 1.1% in the control group (14). Our data confirmed a decrease in ovarian responsiveness to gonadotropins and diminished ovarian reserve in women previously treated for moderate-severe endometriosis (cycle cancellation rate 13.8% in endometriosis stages III–IV vs. 3.6% in endometriosis stages I–II and 3.7% in tubal factor group). In contrast, the fertilization rate in women with severe endometriosis was similar to that in women with tubal factor infertility and higher compared to women with mild endometriosis. This finding is in line with other studies (16,17). Aboulghar et al. hypothesized that one possible reason for this may be that lesions associated with severe endometriosis often do not have active endometrial glands, but instead are 'burned-out' lesions resulting in pelvic adhesions (15).

Women with minimal/mild endometriosis showed a significantly reduced fertilization rate when compared with both stage III–IV and tubal factor. When comparing minimal/mild endometriosis and tubal factor for the other parameters, the result was similar. The negative influence on fertility of moderate and severe endometriosis is plausible because of impaired tubal motility and ovum pick-up function. In cases of minimal/mild endometriosis with no apparent structural damage, the etiological basis for infertility is still unclear. Moreover, stage I–II of endometriosis is usually diagnosed through laparoscopy, and its prevalence among infertile women is probably underestimated.

In the management of fertility problems associated with endometriosis, it is widely accepted that endometriosis stage I–II may be considered equivalent to unexplained infertility and managed accordingly (National Institute for Health and Clinical Excellence guidelines). According to Vercellini et al., minimal/mild endometriosis could represent a temporary phase in an ongoing process that usually results in cytolysis of recently implanted endometrial cells (18).

In contrast, there is evidence that surgical treatment of minimal and mild endometriosis increases fecundity in infertile patients. A systematic review and meta-analysis of two randomized controlled trials (n=444) showed that laparoscopic ablation or resection of minimal and mild endometriosis plus laparoscopic adhesiolysis increased

ongoing pregnancy and live birth rates compared with diagnostic laparoscopy (pooled odds ratio 1.64; 95% confidence interval 1.05–2.57; 19). In a recent study we observed that in stages I and II the first six-month fecundity rate after laparoscopic surgery was 27%, and it was not significantly different from the fecundity rate of 17% of the following six months (months seven to 12). The fecundity rate dropped significantly to 4% after one year, and there were no conceptions after 60months (20). Furthermore, it has been shown that women with mild endometriosis have an increased volume of peritoneal fluid, containing more activated inflammatory factors. Peritoneal fluid can influence reproductive processes by modulating the microenvironment. It seems reasonable that a hostile peritoneal and/or tubal environment may be considered as a possible cause of infertility in women with stage I–II endometriosis (21). In a recent study, Ding et al. observed that when oocytes and embryos were cultured in media with peritoneal fluid obtained from infertile women with mild endometriosis, the fertilization capability of oocytes and the development potential of embryos were decreased. They concluded that endometriotic peritoneal fluid may attenuate oocyte and embryo development by impairing the embryonic growth factor/receptor/signal transduction, resulting in endometriotic infertility (21). Our observation demonstrated that the fecundity rate dropped significantly to 4% one year after surgery. In patients surgically treated for endometriosis, the peritoneal fluid containing activated inflammatory factors might progressively increase after surgery. In this scenario, IVF-ET could act by removing oocytes from a hostile environment.

The strength of the present study is the carefully selected homogeneous groups of patients in both the study and the control groups. By excluding women older than 35 years and/or with clinical/ultrasonographic sign of recurrences at the time of the IVF-ET cycle we obtained two comparable groups. Moreover, women with endometriosis showed fertility problems before surgery, thus not necessarily due to the possible effect of surgery.

The lack of studies conducted on homogeneous groups may be an important reason for confusing and contradictory data in the literature on the effect of endometriosis on IVF-ET outcomes. Limiting a clinical trial to a homogeneous group of participants lessens potential confounders. Obviously, the strict criteria followed for the selection in our study led to a reduction of the number of patients included. In addition, the retrospective analysis and the lack of a diagnostic laparoscopy before IVF-ET in both groups to ascertain the absence of minimal endometriotic lesions might further limit the power of the study. However, it would be unethical to submit these patients to laparoscopy before the IVF-ET cycle.

The cause and effect relation between endometriosis and infertility is difficult to study because of the multiple mechanisms through which endometriosis may interfere with fertility. The IVF-ET cycle consists of several steps, each one of which can be analyzed individually for the effect of endometriosis on reproductive function.

These results suggest that different stages of endometriosis might interfere with IVF-ET outcome through different effects and mechanisms. For moderate/severe stages, we observed the deleterious effect on IVF-ET cycles in terms of cancellation rate, poor responsiveness and implantation rate. Stage I–II showed a significantly impaired fertilization rate.

The ASRM classification proved useful in predicting the outcome of infertility treatment and might be used for planning and counseling purposes. Future research in endometriosis is needed to clarify these mechanisms and should focus on homogeneous groups of patients and stratify results on the basis of ASRM stages. Our results suggest that clinical trials on endometriosis patients need to differentiate between stages (I–II vs. III–IV) to have more homogeneous and nonconfusing data due to different interference of the endometriosis stage on the reproductive outcome or in IVF cycles.

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