ENDOMETRIOSIS

Reduced Developmental Potential in Oocytes From Women With Endometriosis¹

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Submitted: January 3, 2001

Accepted: April 27, 2001

Purpose: To study retrospectively the outcome of intracytoplasmic sperm injection (ICSI) in women with endometriosis compared with women with no known female infertility factor.

Methods: All couples treated with ICSI because of male infertility plus verified endometriosis (n = 26) and all couples treated with ICSI because of male infertility only (n = 125) during the period January 1995 to June 1999 were included. Data were collected from patient files and ICSI protocols.

Results: The time to complete down regulation was significantly longer (p = 0.0108), the dose of FSH significantly higher (0.0247), the day for oocyte pickup significantly later (p = 0.0091), and the cleavage rate of oocytes significantly lower (p = 0.0011) in women with endometriosis compared with controls. There was no significant difference in implantation rate or pregnancy rate between the groups.

Conclusions: Women with endometriosis presented significantly reduced follicular response and oocyte cleavage

rate, two mechanisms that might be related to a disturbed oogenesis.

KEY WORDS: cleavage rate; endometriosis; fertilization rate; ICSI; implantation rate; infertility; pregnancy outcome.

INTRODUCTION

About 60% of women with endometriosis are subfertile (1). The pathophysiology of the subfertility in endometriosis is still unknown, although different mechanisms have been suggested (1). There are several indications of disturbances in the cellular and biochemical environment in the pelvis related to the immune system, which could have a negative influence on the maturation and fertilization of the oocyte, implantation, and the embryo development (2–4). Endometriotic lesions and endometriosis related pain can be treated pharmacologically or surgically. However, pharmacological treatment, usually hormonal, does not improve the endometriosis related subfertility (5). The effect of surgery on the subfertility has been more difficult to study in well-controlled programs. Marcoux *et al.* (6) found in a prospective, randomized study that laparoscopic extirpation of minor endometriotic lesions might improve fertility the first year after treatment. In vitro fertilization (IVF) has become the treatment of choice for endometriosis-related subfertility, as it makes it possible to bypass some of the proposed obstacles. Evaluation of different techniques for assisted procreation might contribute to an understanding of the pathophysiology of endometriosis related subfertility. Several studies

¹ Presented in part at the 4th World Congress on Endometriosis, Quebec, Canada, June 30–July 4, 1998.

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have shown that the pregnancy outcome after IVF in women with endometriosis is similar to that after treatment for other indications (7–9). However, in a previous study (10) we analyzed the outcome of IVF in women with endometriosis compared to women with tubal factor infertility and found a reduced fertilization rate in the endometriosis group, which is in agreement with some other reports (11–13). The pregnancy rate did not differ. This might indicate that the defect is located on the surface of the oocyte or in the interaction between the oocyte and sperm. Cleavage and implantation failures have also been reported when IVF has been applied on patients with endometriosis (13–15). These results all indicate a disturbed oocyte function.

By inserting the sperm into the oocyte, intracytoplasmic sperm injection (ICSI), the fertilization rate could possibly be improved by bypassing mechanisms interacting with fertilization, i.e., factors on the oocyte surface. The aim of this study was to determine whether the early development of the fertilized oocyte is the same in women with and without endometriosis, when the sperm penetration is performed artificially using ICSI because of male infertility.

MATERIALS AND METHODS

During the period from January 1995 to June 1999 702 ICSI-ET (embryo transfer) procedures were performed at our clinic. All couples who underwent ICSI due to male factor infertility, using only spontaneously ejaculated sperm, and only cycles where at least one oocyte was obtained, and who also fulfilled all the other strict inclusion and exclusion criteria mentioned below, were included in the study. Women with a verified endometriosis were included in the study arm and healthy women in the control arm.

During the study period, 26 couples (43 cycles) were treated because of male factor infertility in combination with endometriosis. Endometriosis had been diagnosed previously by laparoscopic visualization and, in cases where convincing diagnosis had not been obtained macroscopically, the diagnosis was verified histologically from a biopsy of the endometriotic implants. None of the women with endometriosis were on hormonal treatment of their endometriosis with either a GnRH agonist, gestagen, or danazol at the time when down regulation for ICSI started. None of the patients included in the study had any indications or signs of an endometrioma visible at ultrasound examination. The mean age was 34 ± 4 years

and the mean duration of infertility was 6 ± 3 years. Most women had primary infertility. Forty-two cycles were performed in women of this category and one cycle was performed in a woman who had been pregnant once before.

The control group consisted of all the 125 cycles in 125 couples with male factor as the only apparent cause of infertility, treated with ICSI during the same period. The mean age was 32 ± 4 years and the mean duration of infertility was 7 ± 3 years. Women with primary infertility contributed with 124 cycles.

No woman with a history of endometriosis was included in the study as a control, but a diagnostic laparoscopy immediately before the ICSI to exclude endometriosis in these women was not allowed for ethical reasons. We had very strict criteria for inclusion in the study. Women with endometriosis and control women were not included if they had a history of, or indications of a tubal disease or previous tubal surgery. No women with ovarian endometriotic cysts that might influence the ovarian function or the ovarian access were included. Most women that had passed an ICSI-ET procedure during the study period belonged to such a mixed diagnosis group and were thus excluded from the study, leaving a limited but very strictly selected homogenous group of comparable women for the study.

The criteria used for male factor was azoospermia and for ejaculated sperm less than 20×10^6 spermatozoa/ml, motility less than 30%, and strict criteria for morphology, including less than 5% normal.

A standard IVF protocol was used. Briefly, treatment started on Cycle Day 1 or 21, equally distributed among the study and control patients, with daily intranasal administration of buserelin acetate (Suprecur® 900–1200 µg/day; Hoechst, Frankfurt, Germany) until the endometrium was less than 4 mm thick according to ultrasound examination and/or serum estradiol <100 pmol/L assayed by RIA (Estradiol Double Antibody, Diagnostic Products Corp., Los Angeles, CA). Ovarian stimulation was achieved by follicle stimulating hormone (FSH, Fertinorm HP®; ARES Serono, Geneva, Switzerland or Gonal-F®, Serono) given daily by subcutaneous self-administration. There was no difference in the distribution of the two drugs in the two patient groups. The starting dose was 150–225 IU, and the dose was adjusted according to the serum estradiol level (assayed by CLIA, Immulite®, Diagnostic Products Corp., Los Angeles, CA) and follicular growth as monitored by ultrasound. The criterion

for administration of 10,000 IU human chorionic gonadotrophin (hCG, Profasi®; Serono) was the presence of at least three follicles larger than 18 mm in diameter. Oocyte pickup (OPU) by transvaginal ultrasound guidance was performed 37 h after the hCG administration. Standard ICSI procedures were used. The minor changes in culture media and different batches over time were equally distributed among the two patient groups. Fertilization was checked after 18–20 h, and cleavage stages evaluated after 44–48 h, of culture. The embryos were graded according to their morphology and cleavage stage on the day of ET (16). A scale of 1–3 was used, with a score of 3.5 for the best embryos. Luteal support was given as 1250 IU hCG on Days 3, 6, 9, and 12 after ET or by progesterone 50 mg/day intramuscularly. Pregnancy was diagnosed by a rising level of serum hCG, which was assayed 14–16 days after ET (16). Clinical pregnancies were determined by ultrasound showing the presence of a gestational sac during the 6th or 7th week after ET. All patients included in this study received the same treatment from down regulation until OPU besides the changes mentioned above.

There is no Institutional Review Board at the hospital, but the study was approved by the local Ethics Committee at Huddinge University Hospital.

Statistical Analysis

The significance of differences found was estimated by the *t* test, Fischer's exact probability test, or by the Mann–Whitney U-test. A *p* level of <0.05 was considered significant.

RESULTS

There was no significant difference in duration of infertility between the two groups, but the women with endometriosis were slightly, but significantly, older than the controls (*P* = 0.04). The time to complete down regulation of the ovaries was significantly longer, the dose of FSH needed was significantly higher, and the day for OPU was significantly later in women with endometriosis compared with controls (Table I). The number of eggs retrieved and the fertilization rate did not differ significantly between the groups, but the cleavage rate was significantly lower in the endometriosis group (Table II). The number and quality of the transferred embryos showed no statistically significant differences between the groups. The ICSI-ET outcome is shown in Table III. The pregnancy rates, implantation rates, and de-

Table I. Results of Stimulation in ICSI-ET Cycles in Women With Endometriosis Compared With Controls (*t* test)

	Endometriosis (Mean ± SD)	Control (Mean ± SD)	<i>P</i>
No. of cycles (patients)	43 (26)	125 (125)	
Down regulation time (days)	39.0 ± 21.1	32.4 ± 10.6	0.0108
Dose of FSH (IU)	2740 ± 1018	2378 ± 857	0.0247
OPU day	30.4 ± 11.5	25.1 ± 11.2	0.0091
E ₂ at hCG (pmol/L)	4217 ± 2703	4437 ± 3079	ns
No. of follicles >10 mm	10.7 ± 5.5	12.0 ± 4.7	ns

Note. ICSI-ET: intracytoplasmic sperm injection–embryo transfer; OPU: ovum pickup, calculated from the first day of FSH administration; hCG: human chorionic gonadotrophin; E₂: estradiol.

livery rates did not differ significantly. There was no difference between the groups concerning sperm quality.

DISCUSSION

This study has shown that oocytes from women with endometriosis treated with ICSI have a significantly lower cleavage rate compared with the cleavage rate of oocytes from women without any known female cause of infertility. Contradictory to our IVF study (10), we did not find any significantly lower fertilization rate, but the present results are in accordance with some other studies on IVF (13,15) that have shown a significantly lower cleavage rate in oocytes from women with endometriosis compared with women with tubal factor infertility. Hull *et al.* (13) found at IVF a significant reduction of both fertilization and cleavage rates in a large, retrospective study of women with endometriosis compared with women with unexplained infertility. This means

Table II. Results of Fertilization and Embryo Development in ICSI-ET Cycles

	Endometriosis (Mean ± SD)	Controls (Mean ± SD)	<i>P</i>
No. of eggs	10.5 ± 6.3	12.2 ± 5.8	ns
No. of fertilized eggs	5.5 ± 3.4	5.8 ± 3.6	ns
Fertilization rate (%)	69.2 ± 25.0	61.4 ± 23.7	ns
No. of cleaved eggs	4.9 ± 3.4	5.6 ± 3.4	ns
Cleavage rates (%)	86.1 ± 20.3	94.5 ± 11.5	0.0011
No. eggs to ET	1.9 ± 0.6	1.9 ± 0.3	ns
Morphologic score of embryo for ET	2.3 (range 1.5–3.0)	2.4 (range 1.2–3.5)	ns

Note. The morphologic score was analyzed by the Mann–Whitney U-test, the other variables by *t* test.

Table III. Analysis of Pregnancy Outcome in Women With Endometriosis Compared With Controls

	Endometriosis	Controls	P
No. of ET	43	122	
No. of positive hCG per OPU (%)	10/43 (23)	41/125 (33)	ns
Implantation rate ^a (%)	12/80 (15)	49/233 (20)	ns
No. of biochemical pregnancies	0	1	
No. of spontaneous abortions	1	5	
No. of ectopic pregnancies	0	2	
Delivered per OPU (%)	9/43 (21) ^b	33/125 (26) ^c	ns

Note. The results were analyzed using the Fischer's exact probability test.

^a Defined as number of embryos implanted according to ultrasound examination.

^b Two twin pairs.

^c Five twin pairs.

that when the sperms are mixed with an oocyte from a women with endometriosis they have difficulties to penetrate and fertilize the oocyte, i.e., the reduced fertilization rate at IVF might be related to problems in the zona pellucida or the oocyte membrane. When the sperm is injected into the oocyte, the fertilization may occur but there are some problems with the cleavage. The reduced cleavage rate found indicates that the disturbance is related to the oocyte itself, i.e., the oocyte can be fertilized mechanically, but does not develop properly. These results indicate that the environment in the follicle is inappropriate and cause an oocyte dysfunction at different levels. Like several previous studies (10,12,15), we did not find any significant difference in implantation rates and pregnancy rates.

The present results are contradictory to the only one previously published study on ICSI and endometriosis (17), that did not show any significant differences in either fertilization or cleavage rate in a large, retrospective study on 980 ICSI cycles, where 101 cycles were from women with endometriosis and the remaining 879 cycles were from women with no signs of the disease. However, that study showed a significant reduction of the number of oocytes retrieved from women with endometriosis compared with controls. It does not appear from that publication whether the control group included women with other factors contributing to the infertility, which might be one explanation for the differences compared with this study. They found a reduced number of oocytes as well, that might indicate a disturbed environment for oocyte development.

We found that a significantly higher dose of FSH was needed and the FSH stimulation had to be given for a significantly longer time, i.e., the OPU day was

significantly later in women with endometriosis compared to controls. These results are in accordance with Huang *et al.* (12) who found that women with all stages of endometriosis required more FSH than those with tubal factor related infertility. Although higher doses of FSH was needed in this study, the resulting estradiol level was not higher and the number of follicles larger than 10 mm were not higher in women with endometriosis, indicating that their follicles were more resistant to stimulation, but when reacting, did develop similar to those in controls. This might be in accordance to Doody *et al.* (18) who found that the follicular growth rate is slower in women with endometriosis compared to healthy controls. This might disturb the synchronization of oocyte maturation and ovulation in these women. This adverse reaction might depend on disturbances in the granulosa cell function. We have found that the production of TNF α from cultivated granulosa cells is significantly higher in women with endometriosis compared to granulosa cells from healthy women undergoing IVF due to male factor infertility (19). Also the production of IL-1 β , IL-6, and IL-8 was elevated. Buyalos *et al.* (20) could not find any significant difference in IL-6 level in follicular fluid from women with endometriosis compared to healthy women after ovarian hyperstimulation, but Pellicer *et al.* (21) found that the level of IL-6 in follicular fluid and the release of IL-6 from granulosa cells was higher in women with endometriosis compared with healthy women. In contrast, the level of released IL-1 β did not differ significantly between the two groups. A disturbed granulosa cell function might create an unfavorable environment for the oocyte. The human oocyte expresses the Type II receptor for TNF α (22), which means that the increased production of TNF α from granulosa cells in women with endometriosis might give deleterious signals to the oocyte. The effect of IL-1 β , IL-6, and IL-8 on the oocyte is not known and their receptors in the oocyte have not to our knowledge been studied.

As the number of embryos obtained per aspirated oocyte sometimes is reduced in women with endometriosis, one crucial factor is the number of oocytes obtained. If enough of oocytes are obtained at puncture, there will often be some that fertilize. The hypothesis that the development of the oocyte is disturbed is strengthened by the results in another publication from the Valencia group (14) that showed a higher pregnancy rate per transfer after donation of oocytes from women without known endometriosis to women with endometriosis, compared to the

pregnancy rate after use of oocytes from the patient herself. When oocytes from women with endometriosis were donated to women without endometriosis, the implantation rate was reduced. Reduced fertilization and cleavage rates remained in women with endometriosis also when spermatozoa from partners were substituted by spermatozoa from donors (13). Support for this hypothesis is also given by J.L.H. Evers, who has scrutinized studies on artificial semen insemination (AIH) and ovarian hyperstimulation (OHS) in women with endometriosis. He found that AIH resulted in lower pregnancy rate in women with endometriosis compared with controls, but after OHS there was no significant difference between groups (personal communication).

These results indicate an oocyte factor involved in endometriosis-related infertility. However, a higher number of oocytes are retrieved after ovarian stimulation compared with that in spontaneous cycles; therefore, the possibility to obtain fertilization of at least one oocyte is higher after ICSI-ET and thus the take-home baby rate is higher. The reason for the oocyte defect is not clear, but a disturbed development of the oocyte in a suboptimal environment in the follicle or the ovarian surroundings might be of importance. The reason for this disturbance is not clear, but an impact from surrounding inflammatory substances with consequences for the paracrine regulation of granulosa cells has to be studied further. There is a large amount of data showing that the peritoneal cavity contains increased levels of different inflammatory substances in women with endometriosis (23–25), and there are some indications of higher levels of IL-6 in women with associated infertility than in nonendometriosis fertile women (26). To which degree the follicular content and ovarian environment is also disturbed is only partly known. We have studied the level of PgF_{2α} in follicle fluid from women with endometriosis and found no difference between women with visible and women with no longer visible endometriosis, at least not concerning this inflammatory mediator (27). The different results from the two studies on ICSI of women with endometriosis might also depend on different frequencies of different stages of endometriosis. As both studies were retrospective, it was not possible to clinically stage the endometriosis at the time for ICSI. As staging had been done at previous laparoscopy, and as the time interval from staging to ICSI varied, the stage might have changed. According to Palmisano *et al.* (28) the anatomic site, type of lesion, and staging of endometriosis is of minor importance for predicting fertility and outcome of assisted

reproduction, but Pal *et al.* (29) in a retrospective study found that the oocytes from women with moderate or severe endometriosis had a significantly lower fertilization rate compared with oocytes from women with minimal or mild endometriosis. As endometriotic ovarian cysts have been regarded as a possible disturbing factor for a successful assisted procreation, an ultrasound examination was performed at the day of OPU. Moreover, this study excluded all women with known ovarian cysts, insufficient diagnostic verification of endometriosis, women on hormonal treatment of their endometriosis just before the start of ovarian down regulation for ICSI and also all cases with mixed indications for ICSI. Thus our study included two strictly controlled and homogenous groups of patients.

One possible contribution to the significant difference between the two studied groups might be the difference in the women's age. However, no other studies have shown that the age difference between 32 and 33 years would result in significantly different cleavage rates.

CONCLUSION

This study indicates that endometriosis affects the follicle response to hormones and cleavage potential after ICSI. This strengthens the hypothesis that the follicular function is disturbed, leading to an oocyte defect in women with endometriosis. The reduced quality of oocytes from women with endometriosis might be related both to factors in the zona pellucida or the oocyte membrane as well as to the cleavage capacity, and might be caused by a pathological content in the follicle; for instance, a different content of cytokines that might disturb the development of the oocyte. The high number of oocytes obtained after ovarian stimulation might explain the higher take-home baby rate compared with that in spontaneous cycles.

ACKNOWLEDGMENTS

Torbjörn Hillensjö is acknowledged for suggestions on study design. The project was supported by The Swedish Medical Research Council (Grant No. K97-17X-09511), Stockholm, Sweden.

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