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The effect of endometriosis on implantation: results from the Yale University in vitro fertilization and embryo transfer program

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Objective: To investigate the effect of endometriosis on implantation.
Design: Case-control study from Yale University IVF-ET program.
Patients: Two hundred eighty-four consecutive IVF cycles were analyzed retrospectively. Patients with endometriosis only (n = 35; 89 cycles) were compared with an age-matched control group with tubal infertility (n = 70; 147 cycles) and also to a group with unexplained infertility (n = 15; 48 cycles). Data from the endometriosis group was analyzed further in subgroups of minimal-mild (43 cycles) and moderate-severe (46 cycles).
Results: No difference was found in the number and the quality of oocytes retrieved and fertilization rates between the endometriosis, the tubal infertility, and the unexplained infertility groups. The quality and the number of embryos transferred in each group were comparable. A trend toward reduced pregnancy rate per transfer (14.8%) in the endometriosis versus tubal or unexplained infertility groups (25.7% and 23.3%, respectively) was observed. Implantation rate (gestational sac per transferred embryo) was significantly lower in the endometriosis versus the tubal infertility group (3.9% versus 8.1%; unexplained infertility group, 7.2%). Analysis of first cycles only across all groups revealed that the implantation rate also was significantly lower in the endometriosis versus the tubal infertility group (3.1% versus 9%; unexplained infertility group, 6.7%). Within the endometriosis group, although the pregnancy rate per cycle and per transfer were similar in subgroups, patients with minimal-mild endometriosis had the lowest implantation rate.
Conclusion: We conclude that, in patients with endometriosis, implantation rate is low. Abnormal implantation, which may be secondary to endometrial dysfunction or embryotoxic environment, is a factor in endometriosis-associated subfertility.
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Key Words: Endometriosis, implantation, IVF-ET success rates, infertility

Endometriosis is a common disease affecting 7% to 50% of reproductive age women (1). Several investigations have generated support for the association between endometriosis and infertility (2), but a specific cause and effect relationship still is debated. Extensive investigations suggest a multifactorial etiology for endometriosis-associated infertility, which includes distortion of pelvic anatomy, abnormalities of hormone secretion (3), impaired fertilization (4), alterations in peritoneal fluid (5), and immunoregulatory dysfunction (6). When endometriosis causes anatomical distortion of the pelvis or obstruction of the fallopian tubes, the result is often infertility. However, the issue that endometriosis alone can cause infertility in the absence of anatomical distortion is controversial. Data from animal (7), as well as human (8), studies have failed to demonstrate diminished fertility in the absence of pelvic adhesions. On the other hand, other studies have shown that pregnancy rates are lower in untreated women with either minimal or moderate (9) endometriosis as compared with treated patients.

In vitro fertilization-ET has become a recognized treatment for refractory endometriosis-associated

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infertility. However, results from IVF-ET cycles also are controversial. Some investigators have demonstrated equally successful outcomes in these patients compared with patients with other causes for their infertility (10, 11). In contrast, other authors have reported a poorer outcome (12). Two different mechanisms have been postulated for the poor outcome observed in patients with endometriosis: decreased fertilization rates (4) and/or defective implantation of the embryos (13). Immunologic disturbances in women with endometriosis may affect the gametes and embryos. Thus, impaired fertilization (14), embryotoxicity (15), and defective implantation (13) are proposed as consequences of immunologic disturbances in these patients.

The present study was undertaken to investigate the implantation success in patients with endometriosis compared with a group with tubal disease and a group with unexplained infertility in our IVF-ET program. We compared IVF parameters, including oocyte number and quality, fertilization, implantation, and pregnancy rates in women with or without endometriosis and evaluated the effect of the stage of endometriosis on these parameters.

MATERIALS AND METHODS

We reviewed medical records of all patients undergoing IVF procedures in our program at Yale-New Haven Hospital between January 1988 and May 1994. The protocol for the medical record review was approved by the Human Investigation Committee of this University. A retrospective analysis of 284 IVF cycles from patients with the only diagnosis of endometriosis, or tubal factor, or unexplained infertility were performed: a total of 89 cycles corresponding to 35 patients with different stages of endometriosis, a control group consisting of 147 cycles corresponding to 70 patients with tubal factor infertility, and a group consisting of 48 cycles corresponding to 15 patients with unexplained infertility. All the patients had a laparoscopy before the procedure and underwent complete infertility evaluation including BBT recordings, midluteal endometrial biopsy, and/or serum P levels, hysterosalpingogram, postcoital test, semen analysis of the male partner, and antisperm antibody testing, if indicated. Normal sperm parameters was defined as at least two sperm analyses with count $> 20 \times 10^6$ sperm/mL, motility $> 50\%$, and morphology defined as $>50\%$ normal forms. Endometriosis was confirmed by direct laparoscopic visualization and/or biopsy of lesions. The severity of the disease was staged as defined by the revised American Fertility Society classification (16) and divided into two subgroups as minimal to mild (stages I and II; 43 cycles in 18 patients) and moderate to severe (stages III and IV; 46 cycles in 17 patients). Tubal damage was defined by laparoscopic evidence of bilateral tubal occlusion not due to endometriosis. Unexplained infertility was defined by normal findings in the above mentioned infertility evaluation that includes normal laparoscopic findings.

A standard IVF protocol was used. Briefly, GnRH-agonist (leuprolide acetate [LA]; Tap Pharmaceuticals, Deerfield, IL) was administered 1 mg/d SC, starting in the midluteal phase of the preceding cycle or first day of the stimulation cycle. Stimulation with hMG (Pergonal or Metrodin; Serono Laboratories, Norwell, MA) was initiated when there was no sonographic evidence of ovarian follicular activity and serum E_2 level was <50 pg/mL (conversion factor to SI unit, 3.671) and was continued until E_2 levels reached ≥ 500 pg/mL and at least two follicles of ≥ 18 mm in diameter were present. At that time 10,000 IU hCG (Profasi; Serono Laboratories) was administered and LA and hMG were discontinued. Oocyte retrieval by transvaginal ultrasound guidance was performed at approximately 34 hours after hCG administration. Oocyte maturity was graded by the morphological appearance of the oocyte-cumulus complex. Oocytes and spermatocytes were incubated at 37°C in 5% CO_2 and air. Embryos were graded (I to V) on the day of transfer according to their morphology under the inverted microscope and transferred transcervically into the uterus. Pregnancies were diagnosed by a rising concentration of serum β-hCG test, which was performed 14 days after ET. Clinical pregnancies were determined by the presence of a gestational sac on vaginal ultrasound examination during the 5th week.

Data were expressed as means ± SD. For statistical comparison among groups, Student's t-test, χ^2 test, and Fisher's exact t-test were used. P value < 0.05 was considered significant. The statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) Version 6.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Data from 120 consecutive couples that fit the inclusion criteria for one of the three groups were analyzed. Table 1 compares the IVF parameters of patients with endometriosis, patients with tubal infertility, and patients with unexplained infertility. The number and the maturity of the oocyte-cumulus complexes retrieved were not different between the groups. Fertilization rates were similar between endometriosis, tubal factor, and unexplained infertility groups (70.8%, 70.1%, and 66.8%, respectively; P = not significant). The grades of embryos and the

Table 1 Analysis of IVF Cycles in Women With Endometriosis, Tubal Factor, and Unexplained Infertility*

	Endometriosis				
	Total	Stages I and II	Stages III–IV	Tubal factor	Unexplained
No. of cycles	89	43	46	147	48
No. of cases	35	18	17	70	15
Age (yr)	33.8 ± 4.0	34.6 ± 3.7	33.1 ± 4.1	33.1 ± 4.4	34.2 ± 2.8
E_2 (pre-hCG) (pg/mL)†	1,203 ± 718‡	1,485 ± 815§	946 ± 497§	1,466 ± 1,064‡	1,311 ± 874
No. of oocytes retrieved per cycle	8.1 ± 5.9	11.0 ± 6.1§	5.3 ± 4.2§	9.5 ± 7.3	7.7 ± 4.3
Average oocyte quality	2.6 ± 0.7	2.8 ± 0.5	2.5 ± 0.8	2.7 ± 0.6	2.4 ± 0.5
No. of oocytes fertilized per cycle	5.7 ± 4.3	7.4 ± 4.2§	4.2 ± 3.8§	6.7 ± 5.5	5.2 ± 3.7
Fertilization rate (%)	70.8	66.8§	78.4§	70.1	66.8
No. of transfers	81	42	39	136	43
No. of embryos transferred per cycle	3.8 ± 1.6	4.3 ± 1.5‖	3.3 ± 1.6‖	3.9 ± 1.4	3.6 ± 1.2
Average embryo quality	1.9 ± 0.6	1.8 ± 0.5	2 ± 0.6	1.9 ± 0.5	1.8 ± 0.6

* Values are means ± SD.
† Conversion factor to SI unit, 3.671.
‡ Significantly different, $P = 0.026$.
§ Significantly different, $P < 0.001$.
‖ Significantly different, $P = 0.006$.

total number of embryos transferred in each group were comparable.

Table 2 compares the IVF outcome between the groups. There were 12 pregnancies in the 89 endometriosis cycles. The data showed a trend toward reduced pregnancy rate per transfer among the patients with endometriosis compared with tubal factor cases (14.8% versus 25.7%, $P = 0.058$; unexplained infertility: 23.3%, $P = 0.24$). Implantation rate (gestational sac per transferred embryo) was significantly lower in the endometriosis versus tubal infertility group (3.9% versus 8.1%, $P = 0.017$; unexplained infertility group, 7.2%, $P = 0.12$).

When the data were analyzed according to the stage of endometriosis (16) (Tables 1 and 2), stage III and IV cases revealed a significantly higher fertilization rate than stage I and II cases (78.4% versus 66.8%; $P = 0.001$), but implantation rate was low and not significantly different between the subgroups (stages III and IV: 5.5% and stages I and II: 2.8%; $P = 0.46$).

To eliminate bias from repeated IVF attempts, we separately analyzed data limited to the first cycle of each patient (Table 3). The implantation rate was significantly lower in the endometriosis group compared with the tubal factor group (3.1% versus 9%; $P = 0.03$), despite better fertilization rates (77.8% versus 71.4%; $P = 0.04$). In the unexplained infertility group, the fertilization rate was significantly lower than endometriosis group (52.5% versus 77.8%; $P < 0.001$). Despite the lower fertilization rate, the implantation rate of the unexplained infertility group was twofold higher than the endometriosis group (6.7% versus 3.1%; $P = 0.26$).

DISCUSSION

Endometriosis is associated with marked subfertility as shown by the comparison of cumulative con-

Table 2 Analysis of IVF Outcome in Women With Endometriosis, Tubal Factor, and Unexplained Infertility

	Endometriosis				
	Total	Stages I and II	Stages III and IV	Tubal factor	Unexplained
No. of pregnancies	12	5	7	35*	10
No. of gestational sacs	12	5	7	43	11
Pregnancy rate per patient	12/35 (34.3)‡	5/18 (27.7)§	7/17 (41/4)	35/70 (50)	10/15 (66.7)‡§
Pregnancy rate per cycle	12/89 (13.5)	5/43 (11.6)	7/46 (15.2)	35/147 (23.8)	10/48 (20.8)
Pregnancy rate per transfer	12/81 (14.8)	5/42 (11.9)	7/39 (17.9)	35/136 (25.7)	10/43 (23.3)
Implantation rate	12/308 (3.9)‖	5/180 (2.8)¶	7/128 (5.5)	43/531 (8.1)‖¶	11/152 (7.2)
Abortion rate	5/12 (41.7)	2/5 (40)	3/7 (42.9)	9/35 (25.7)	4/10 (40)
Deliveries per patient	7/35 (20)	3/18 (16.7)	4/17 (23.5)	25/70 (35.7)	6/15 (40)
Deliveries per cycle	7/89 (7.9)**	3/43 (7)	4/46 (8.7)	25/147 (17)**	6/48 (12.5)
Deliveries per transfer	7/81 (8.6)	3/42 (7.1)	4/39 (10.3)	25/136 (18.4)	6/43 (14)

* One ectopic pregnancy.
† Values in parentheses are percentages.
‡ Significantly different, $P = 0.034$.
§ Significantly different, $P = 0.025$.
‖ Significantly different, $P = 0.017$.
¶ Significantly different, $P = 0.013$.
** Significantly different, $P = 0.046$.

Table 3 Analsysis of the First Cycle IVF Outcome in Women With Endometriosis, Tubal Factor, and Unexplained Infertility*

	Endometriosis (all stages)	Tubal factor	Unexplained
No. of cycles	35	70	15
E_2 (pre-hCG) (pg/mL)†	1,235 ± 709	1,519 ± 1,157	1,593 ± 1,089
No. of oocytes retrieved per cycle	8.2 ± 4.9	10 ± 7.8	8 ± 5.1
No. of oocytes fertilized per cycle	6.4 ± 4.3	7.1 ± 6.2	4.2 ± 3.2
Fertilization (%)	77.8‡§	71.4‡	52.5§
No. of transfer cycles	34	66	12
No. of embryos transferred per cycle	3.8 ± 1.3	3.9 ± 1.3	3.8 ± 0.9
No. of pregnancies	4	20	3
Pregnancy rate per transfer (%)	4/34 (11.8)‖	20/66 (30.3)‖	3/12 (25)
Implantation rate (%)	4/128 (3.1)‖	23/255 (9.0)‖	3/45 (6.7)

* Values are means ± SD.
† Conversion factor to SI unit, 3.671.
‡ Significantly different, $P = 0.04$.
§ Significantly different, $P < 0.001$.
‖ Significantly different, $P = 0.03$.

ception rates between patients with untreated endometriosis and controls. The development of the IVF-ET technique has provided a new therapeutic approach to endometriosis. However, results are quite controversial. Two initial reports (10, 17) indicated that regardless of whether endometriosis or tubal disease was the indication for IVF, pregnancy rates were comparable. Subsequently, some authors (4) reported a significant decrease in the fertilization rate in women with endometriosis. However, other authors showed no difference in the fertilization rate in patients with endometriosis compared with patients with other indications (18–21). Pregnancy rates were comparable in women with or without endometriosis according to some reports (19, 21) but were lower according to others (22). In our study, we find that, in patients with endometriosis, the number of oocytes retrieved and fertilization rates were similar to patients with tubal factor as others also have shown (12) and a similar number of embryos were transferred. In our study, pregnancy rates per cycle and per transfer also were similar in patients with or without endometriosis. In agreement with Inoue et al. (19) and Dmowski et al. (21), we did not find a significant difference between pregnancy rates and the stage of endometriosis, but, interestingly, we observed a trend toward higher pregnancy rates per cycle and per transfer in advanced stages of endometriosis, suggesting a more important role for the anatomical distortion of the pelvis found in these advanced stages that is bypassed during IVF-ET.

Our study indicates that patients with endometriosis have a lower implantation rate than patients with tubal infertility, a finding that is supported by other authors (20). In the unexplained infertility group, we observed an implantation rate between the endometriosis and the tubal factor group. We summarize in Table 4 the results of previous investigations of the effect of endometriosis on pregnancy rates in IVF. One of the reasons for the controversial results found in the literature probably is due to the difference in the selection of the control group. In some studies, control groups were women with a history of treated endometriosis but with "normal" pelvis at the time of oocyte retrieval (11, 18). If some pathologic processes produce both endometriosis and decreased implantation, removal of endometriotic implants will change only the appearance of the disease without affecting the real pathology. Thus, these patients may not be an appropriate control group. We could find only three previous studies in major literature specifically looking to the implantation rate in endometriosis (4, 20, 23). The consensus opinion presented in these studies is that implanta-

Table 4 The Effect of Endometriosis on Pregnancy Rate and Implantation After IVF: Review of Literature

	No. of cycles per no. of patients		Pregnancy rate per transfer		Implantation rate	
Author (year)	Endometriosis	Control	Endometriosis	Control	Endometriosis	Control
			%		%	
Jones et al. (1984) (10)	20/11	454/249*	40	24	—	—
Chillik et al. (1985) (18)	24/18	15/8†	33.3	33	—	—
Yovich et al. (1988) (23)	57/30‡	40/28*	1.9§	17.5§	0.9§	8.2§
Oehninger et al. (1988) (11)	226/113	54/23†	26.7	20	—	—
Mills et al. (1992) (4)	67/67	122/122*	27	29	12	14
Inoue et al. (1992) (19)	476/309	701/372‖	30.9	27	—	—
Simon et al. (1994) (20)	96/59	78/96*	15.1§	37.3§	5.8§	13.4§
Dmowski et al. (1995) (21)	119/84	118/109‖	29	25	—	—
Arici et al. (1995)	89/35	147/70*	14.8	25.7	3.9§	8.1§

* Control group is women with tubal factor infertility.
† Control group is women with previous history of but treated endometriosis.
‡ Only stage IV endometriosis.
§ Statistically significant difference.
‖ Control group is women with all other indications of IVF.

tion rate is lower in patients with endometriosis compared with other patients. The relationship between the embryo and the endometrium seems to be impaired in patients with endometriosis, but the responsible mechanism for this impairment remains to be elucidated. Recently, aberrant integrin expression in the native endometrium was found to be associated with the presence of endometriosis and that may suggest a defect in uterine receptivity (24). Although an impaired implantation milieu cannot be ruled out, oocyte donation program data from Simon et al. (20) suggest alterations within the oocyte itself, manifested by a reduced implantation capability. On the other hand, Dmowski et al. (21) suggest that autoimmune phenomena may play a negative role in implantation because autoantibody positive patients had similar IVF parameters, but lower pregnancy rates. Immunologic alterations that are present in endometriosis also may be associated with early embryonic rejection or loss. Damewood et al. (15) showed that serum and peritoneal fluid from endometriosis patients was toxic to the development of two-cell mouse embryos in vitro and a short glucocorticoid treatment during the IVF procedure was suggested (25).

We conclude that abnormal implantation that may be secondary to endometrial dysfunction or embryotoxic environment is a factor in endometriosis-associated subfertility. Although we have provided evidence about the association between endometriosis and decreased implantation, the proof of cause and effect still is lacking. Thus, the possibility exists that some pathologic process produces both endometriosis and decreased implantation.

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