Endometriosis Is Not Detrimental to Embryo Implantation in Oocyte Recipients[1]

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Purpose: *Our purpose was to determine the effects of endometriosis on implantation and pregnancy rates in ovum recipients.*
Methods: *The medical records of 239 consecutive oocyte recipient patients who were treated between January 1, 1991, and June 30, 1995, were analyzed retrospectively. Recipients with endometriosis (group I; n = 55) were compared to recipients without endometriosis (group II; n = 184). Patients in group I had active endometriotic disease confirmed by laparoscopy and were subdivided into mild (Stages I and II; n = 18) and moderate to severe (Stages III and IV; n = 37) endometriosis.*
Results: *No difference was found in recipient age, endometrial thickness, donor age, and embryos transferred. The pregnancy rates (28 versus 29%) and implantation rates (12 and 13%) were also comparable between group I and group II, as well as between patients with mild and patients with moderate to severe endometriosis.*
Conclusions: *The presence of endometriosis in oocyte recipients does not lower implantation or pregnancy rates. We conclude that the adverse effect of endometriosis on reproductive outcome is not related to implantation but, in fact, is most likely an effect on oocyte or embryo quality.*

KEY WORDS: endometriosis; implantation; ovum donation; pregnancy.

INTRODUCTION

A range of physiologic and clinical manifestations of endometriosis has challenged gynecologists since the first description of endometriosis as a clinical entity in 1927 (1). Theoretical mechanisms through which endometriosis causes infertility are multifold. Explanations range from the obvious mechanical interference of ovum pickup by adhesions to more subtle ovulatory dysfunction, endocrine dysfunction, and increased sperm phagocytosis from peritoneal factors. Decreased fertilization, defective tubal gamete–embryo transport, and early implantation failure may also be due to endometriosis-related hormonal or autoimmune phenomena (2). The multifactorial nature through which endometriosis causes infertility adds to the challenge of treating this enigmatic disease in a directed and effective manner.

In vitro fertilization of oocytes and subsequent transcervical embryo transfer (IVF-ET) is often used to overcome endometriosis-related tuboadhesive disease. Several investigators, however, report lower than predicted rates of reproductive success using assisted reproductive technologies in the treatment of endometriosis (3–5). The decreased fertility rates in these reports may be attributed to the toxic effects of endometriosis on oocytes and embryos. Others suggest that various immunological factors may interfere with implantation, thereby limiting the effectiveness of IVF (6,7).

We undertook our study to understand better the relationship between endometriosis and endometrial receptivity. In order to control for any confounding effects of endometriosis on gamete or early embryo quality, we derived our population from a cohort of ovum recipients. By controlling for oocyte, sperm, and embryo quality, we are able to answer the question of whether endometriosis adversely affects embryo implantation.

MATERIALS AND METHODS

A retrospective analysis was performed on 239 consecutive oocyte recipients entering the Mount Sinai

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Medical Center Assisted Reproductive Technology program between January 1, 1991, and June 30, 1995. We classified the 239 patients into two groups based on the presence or absence of endometriosis. Diagnosis of endometriosis was confirmed laparoscopically within 2.7 ± 2.4 years (mean ± SD) of the embryo transfer. Staging was performed according to the revised criteria of the American Fertility Society classification (8). Group I consisted of 55 first cycles of recipient women with active endometriotic disease; 53 had ovulatory cycles; the remaining 2 underwent multiple operations for severe endometriosis and were on hormone replacement therapy. Group II consisted of 184 first cycles in recipient women with no evidence of endometriosis identified by a thorough history (absence of cyclical pelvic pain, bowel/bladder symptoms, and family history), physical examination (absence of uterosacral/cul-de-sac nodularity, fixed pelvic organs, and adnexal masses/tenderness), transvaginal ultrasonography (to rule out endometriomas), and/or laparoscopy.

Oocyte donors underwent controlled ovarian hyperstimulation as described previously (9). After midluteal pituitary down-regulation with GnRHa (leuprolide acetate, Lupron; TAP Pharmaceuticals, Deerfield, IL), gonadotropin stimulation was started with hMG (Humegon; Serono Laboratories, Randolph, MA) alone or in combination with FSH only (Metrodin; Serono Laboratories). Criteria for human chorionic gonadotropin (Profasi; 10,000 IU; Serono Laboratories) administration included the presence of two or more follicles greater than or equal to 18 mm in diameter and a serum estradiol level greater than 1000 pg/ml. Transvaginal ultrasound-guided oocyte retrieval was performed 36 to 38 hr later.

Preparation of the endometrium in ovum recipients was also performed as described previously (10). Recipients with ovarian function first underwent pituitary suppression with GnRHa, leuprolide acetate. All ovum recipients then received estrogen replacement (Estraderm; CIBA Pharmaceutical Co., Summit, NJ; 0.2 to 0.4 mg/day; or Estrace; Mead Johnson, Evansville, IN; 2–9 mg/day) for 2 to 4 weeks, with titration of dosage performed to achieve an endometrial thickness of at least 6 mm. The estrogen dosage was continued for 7 weeks after transfer in cases with pregnancy. Progesterone supplementation (vaginal suppositories, 600 mg/day, or im, 50 mg/day; Carter–Glogan Laboratories, Phoenix, AZ) was administered daily beginning on normalized day 15 and continued for 8 to 9 weeks after transfer in patients with positive pregnancy tests. Embryo transfer was performed 48 hr after oocyte retrieval (normalized Day 17 or Day 18) in recipients (10). Cumulative embryo scores were calculated as described previously (11). Embryo grading was performed according to the Veeck clinical classification system (12).

The implantation rate was calculated as the total number of gestational sacs per total number of embryos transferred. We defined pregnancy rate as the presence of a gestational sac on transvaginal ultrasound along with a serially rising serum β-hCG 21 days after the embryo transfer.

Statistical analysis was performed using the software StatView 4.01 (Abacus Systems, Berkeley, CA). Continuous variables were assessed using Student's *t* test. Categorical variables, including implantation and pregnancy rates, were assessed by chi-square test or two-tailed Fisher exact test in the case of small cell frequencies. This study had an 80% power to detect a 25% difference in implantation rate (two-tailed) given an α level of 0.05.

RESULTS

Demographic and first-cycle characteristic data of 239 consecutive recipients are presented in Fig. 1. In the comparison between group I and group II, we find no statistical difference in recipient age (41.8 ± 4.3 vs 41.5 ± 5.6 years) or endometrial thickness (9.5 ± 3.0 vs 8.8 ± 2.2 mm). The donor age (27.1 ± 3.7 vs 27.0 ± 3.0 years) and cumulative embryo score (53.8 ± 36.0 vs 56.6 ± 34.9) are also comparable. The number of embryos transferred (3.2 ± 1.0 vs 3.4 ± 1.5), pregnancy rates (28 vs 29%), and embryo implantation rates (12 vs 13%) are not statistically different between group I and group II, respectively.

Recipients are further subdivided into women with mild endometriosis (Stages I and II; $n = 18$) and moderate to severe endometriosis (Stages III and IV; $n = 37$) in Table I. There is no difference in pregnancy rates among patients with various stages of endometriosis, nor is a difference noted in patients in group I versus group II.

In comparing group I and II recipients with pregnancies ($n = 72$) and without pregnancies ($n = 167$), we find that the endometrial thickness (9.1 ± 2.3 vs 8.7 ± 3.0 mm) is comparable but that the cumulative embryo score (73.2 ± 40.0 vs 57.5 ± 35.0; $P < 0.005$) is significantly higher in the pregnancy group.

DISCUSSION

Endometriosis causes infertility through direct effects on oocyte and embryo quality but has been also

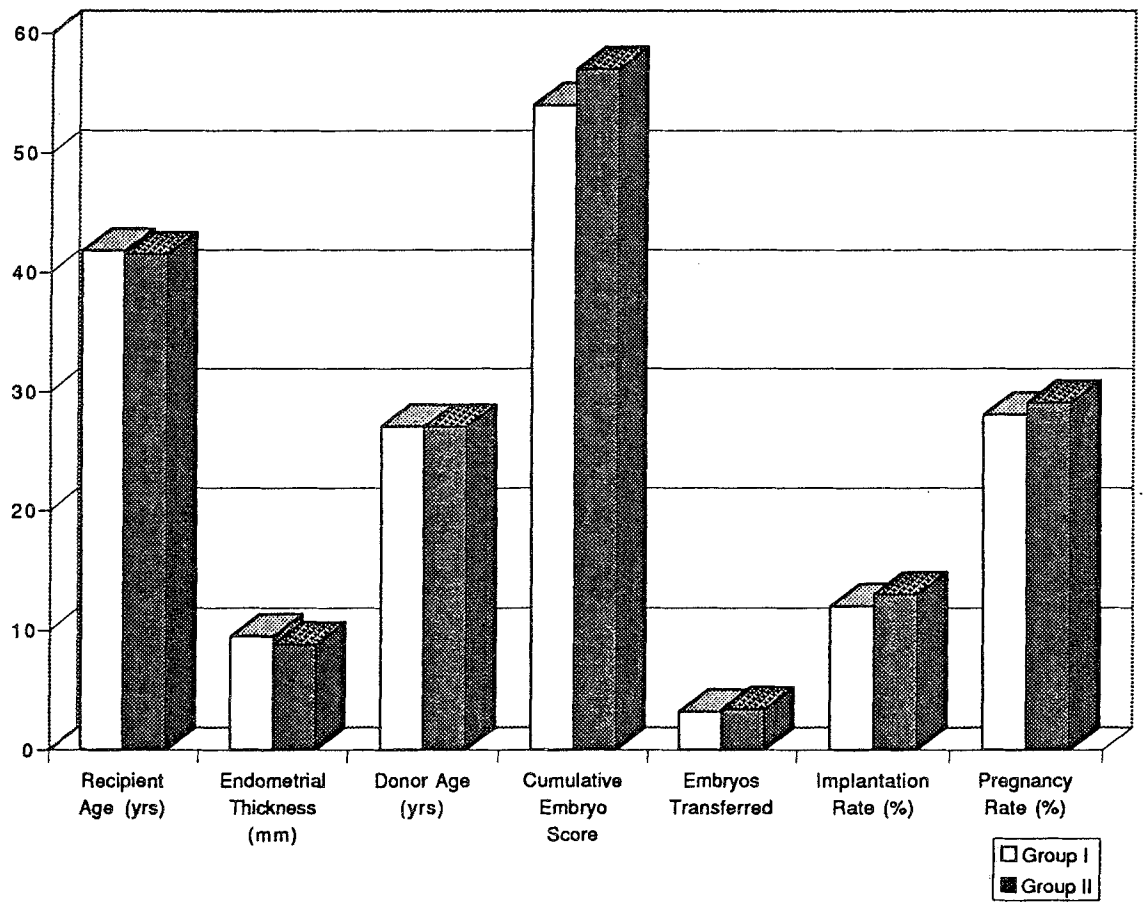

Fig. 1. Demographics and first cycle characteristics.

theorized to affect implantation by immune mechanisms. Identification of any direct effect on implantation is difficult to isolate, due to the limitations of the known confounding adverse effects of endometriosis on gamete quality. In our study, we were able to eliminate these confounding effects by studying a population of ovum recipients, some of whom have been previously diagnosed as having endometriosis and others who have not. Our ovum donors were selected if there was no evidence of endometriosis through history, physical examination, transvaginal ultrasonography, and/or laparoscopy. While this may not definitively exclude endometriosis as a diagnosis, it is likely that these donors may, at worst, have mild disease and, based on our methodology, should be evenly distributed between the groups examined in this study. In addition, patients with mild endometriosis have comparable pregnancy rates when compared to those

Table I. Pregnancy Rates Among Recipients with Mild Endometriosis (Stages I and II) Versus Moderate to Severe Endometriosis (Stages III and IV)[a]

	Stages I & II (n = 18)	Stages III & IV (n = 37)	Total with endometriosis (n = 55)	Total with no endometriosis (n = 184)	Total (n = 239)
Pregnancy	7	8	15	53	68
No pregnancy	11	29	40	131	171

[a] Using the chi-square test, no statistical significance was found when comparing the different groups.

with tubal disease (13,14). Some investigators have even found no difference in pregnancy rates when comparing patients with and without endometriosis (15,16). Through an analysis of 239 first consecutive cycles in oocyte recipients, we find no difference in implantation or pregnancy rates in patients with and without endometriosis and conclude that any potential adverse effects on endometriosis must be exerted at the gamete and embryo level.

To date, few studies in the literature have attempted to evaluate the efficacy of assisted reproductive technology in women with endometriosis on implantation, and all report lower implantation rates (3,12,17,18). Commonly, investigators attribute the decrease in implantation and pregnancy rates due to impaired gamete quality (3–5,19). Most recently, Arici *et al.* demonstrated lower implantation rates in women undergoing first cycles of IVF for endometriosis compared to patients with tubal-factor or unexplained infertility (3.1, 9.0, and 6.7%, respectively) (18). The authors attributed the decreased fertility in the endometriosis group to the defects in uterine receptivity, since oocyte quality, fertilization rates, and number of embryos transferred were similar in patients with endometriosis versus those with tubal and unexplained infertility. In fact, in first cycles, patients with endometriosis had increased fertilization rates compared to those women with tubal-factor or unexplained infertility (77.8, 71.4, and 52.5%, respectively). In contrast, a small series by Simón *et al.* found comparable implantation and pregnancy rates between recipients with and those without endometriosis provided that their donors had no definitive diagnosis of endometriosis (17). However, when the results of oocyte donation were classified according to the origin of the oocytes donated, they found that recipients who received embryos derived from endometriotic ovaries had a significantly reduced implantation rate compared to those with embryos from nonendometriotic ovaries. Simón *et al.* suggested that the decreased fertility in endometriosis patients is due to oocyte quality rather than uterine receptivity. In our study, we expanded upon their preliminary findings and compared pregnancy and implantation rates in recipients with and without active endometriosis utilizing gametes from donors with no history, clinical symptoms, or ultrasonographic evidence of endometriosis. Our findings suggest that uterine receptivity in women with endometriosis is not impaired.

The precise mechanism through which endometriosis interferes with fertility remains to be elaborated. Studies propose possible effects of cytokines, antibodies, and endometrial receptor defects on both gametes and endometrium (2,7,20). Cytokines such as interleukin-1 and tumor necrosis factor-α appear to inhibit embryonic development (20). Higher quantities of these factors have been found in the peritoneal fluid of women with endometriosis (21–24), and treatment of endometriosis decreases the level of cytokines, which results in decreased embryo toxicity (20). Other proposed mechanisms through which endometriosis can impair fertility include autoantibodies adversely affecting embryo implantation (16) and endometrial receptor defects such as a deficiency of the integrin, $\alpha v\beta 3$ (7).

While much has been learned about the epidemiology, diagnosis, and treatment of endometriosis over the past century, a full understanding of its pathogenesis and pathophysiology remains to be uncovered. In our study, we conclude that the presence of endometriosis in oocyte recipients does not affect pregnancy or implantation rates. By using donor gametes, we have controlled for the effects of endometriosis on oocytes and preimplanted embryos. We conclude that in patients with endometriosis, oocyte and embryo factors are more detrimental to female fecundity than implantation factors.

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