Does Surgical Management of Endometriosis Within 6 Months of an In Vitro Fertilization–Embryo Transfer Cycle Improve Outcome?¹

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Purpose: To assess the effect on cycle outcome of surgery for endometriosis performed in the 6 months prior to in vitro fertilization–embryo transfer (IVF-ET).

Methods: Retrospective analysis of all patients with a primary diagnosis of endometriosis undergoing IVF-ET during 12 consecutive months. The setting included tertiary care assisted reproductive technology program. Ninety-five consecutive cycles in candidates for autologous IVF-ET who had undergone surgical resection of endometriosis within 60 months of oocyte retrieval were evaluated. Five patients with persistent or recurrent endometriomas >3 cm at the time of IVF-ET were excluded. Patients were divided into two groups based on the interval between the most recent surgical intervention and oocyte aspiration—Group I: ≤6 months' interval (19 cycles); Group II: >6 months' interval (76 cycles).

Results: Mean intervals between surgery and oocyte aspiration were significantly different between the groups (Gr I: 3.7 ± 0.3 months; Gr II: 21.8 ± 1.6 months; $p < 0.001$). There were no significant differences between groups with regards to age, extent of endometriosis, or results of ovarian stimulation and oocyte aspiration. Ongoing pregnancy rates (Gr I: 63.2%; Gr. II: 60.5%) were similar. Regression analyses revealed no correlation between implantation rates and either endometriosis score ($r = -0.09$) or surgery–oocyte aspiration interval ($r = -0.13$).

Conclusions: The interval between surgical management of endometriosis and oocyte aspiration did not have an impact on IVF-ET cycle outcome in the absence of significant persistent or recurrent ovarian disease. Any effect of surgery on enhancing spontaneous conception may be overcome by the inherently greater impact of IVF-ET on implantation and pregnancy.

KEY WORDS: Endometriosis; in vitro fertilization; laparoscopy.

In vitro fertilization–embryo transfer (IVF-ET) has been well established as a highly successful approach to the treatment of infertility associated with endometriosis(1,2). This task may be achieved by not

only bypassing anatomic distortion but also by avoiding a peritoneal environment which may inhibit normal processes of fertilization, embryo development, and implantation (3,4). Surgical management has been a traditional means of treating endometriosis-related infertility despite a relative dearth of prospective randomized trials. Resection or ablation at laparoscopy or laparotomy may improve short-term pregnancy rates in patients with all stages of disease (5–7). In these studies the majority of spontaneous pregnancies occurred within 6 months of surgical intervention. Others have suggested that surgical

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intervention may not only correct anatomic distortion but may decrease the inhibitory effect of maternal serum on oocyte fertilization and embryo development (8). Thus, in the current investigation, we evaluate the potential effect of endoscopic surgical management of endometriosis performed in the 6 months prior to IVF-ET on enhancing cycle outcome.

METHODS

This analysis is the result of a retrospective review of 95 consecutive IVF-ET patients with a primary diagnosis of endometriosis undergoing a fresh IVF-ET cycle with their own oocytes over a 12-month period performed in a single tertiary care assisted reproductive technology program. All patients had undergone laparoscopic surgical resection or ablation of endometriosis within 60 months of the date of oocyte aspiration. Only those patients who had undergone surgery performed by one of the authors or who had a detailed operative report clearly describing extent of disease as well as technique and extent of surgical resection or ablation were included. Patients were divided into two groups: those who had undergone surgical therapy within 6 months of oocyte aspiration (Group I) and those who had undergone surgical therapy greater than 6–60 months of oocyte aspiration (Group II).

All patients were noted to have an early follicular phase serum FSH level <12 mIU/mL and had at least six resting antral follicles as evaluated by prior ultrasound examination during the mid-follicular phase. A normal endometrial cavity was confirmed by precycle hysteroscopy in all patients. Patients who had been administered a GnRH agonist as treatment for endometriosis within 6 months of oocyte aspiration or those with evidence of persistent or recurrent ovarian endometriotic cysts >3 cm in total mean diameter at cycle initiation were excluded from this investigation. Five patients, all of whom had undergone surgical resection greater than 6 months prior to oocyte aspiration, met this latter exclusion criteria. No patients had undergone prior IVF cycles at the Colorado Center for Reproductive Medicine.

Controlled ovarian hyperstimulation consisted of standard downregulation with a GnRH agonist (Lupron, TAP Pharmaceuticals, Waukegan, IL) 0.5 mg SC daily for 7 days initiated in the midluteal phase prior to gonadotropin stimulation. Other patients received a microdose flare regime as previously described (9). The specific stimulation regimen

selected for each patient was based upon prior response, number of resting antral follicles, and the results of evaluation of ovarian reserve.

Follicular maturation was evaluated by serial ultrasound examinations and measurements of serum estradiol, LH, and progesterone levels. Human chorionic gonadotropin (hCG) was administered when at least one follicle had achieved a mean diameter of 19 mm and serum estradiol levels of at least 500 pg/mL were reported. Transvaginal ultrasound guided oocyte aspiration was performed 35 h after hCG administration. The details and indications for oocyte insemination or intracytoplasmic sperm injection (ICSI) and embryo culture techniques in our program have been previously described (10).

Embryo transfers were performed either 3 or 5 days after oocyte aspiration under ultrasound guidance using an Edmunds–Wallace catheter (Marlow Technologies, Willoughby, Ohio) as previously described (11). Recommendations regarding the number of embryos to be transferred were based upon standard guidelines. Initial serum pregnancy tests were performed 14 days after oocyte aspiration. Ultrasound documentation of the number of gestation sacs and presence of fetal cardiac activity was performed approximately 5–6 weeks after embryo transfer.

Ongoing pregnancy rates were defined as the presence of cardiac activity visualized sonographically per cycle initiated. Implantation rates were defined as number of fetal poles with cardiac activity per embryos transferred. Data were evaluated by Student's group *t*-tests, regression analyses, and chi-square analyses with correction factors employed as appropriate. Unless otherwise indicated, the results are expressed as mean $\pm$ standard error of the mean (SEM). A *p*-value <0.05 was considered to be statistically significant. Because of the retrospective nature of this investigation, institutional review board approval was not deemed necessary.

RESULTS

Baseline clinical data are displayed in Table I. There were no significant differences between the groups with regards to mean age, Day 3 serum FSH levels, or extent of endometriosis described at baseline laparoscopy. The incidence and mean total diameters of ovarian endometriotic cysts resected at those procedures was not significantly different between the groups (Group I: 26.3%, 3.8 ± 0.8 cm; Group II: 18.4%, 2.9 ± 0.5 cm). The incidence of procedures in

Table I. Baseline Clinical Data

Group	Cycles	Age	Day 3 FSH (mIU/mL)	Surgery–oocyte aspiration interval (months)	Endometriosis score ^a
I	19	34.1 ± 0.8	7.03 ± 0.29	3.74 ± 0.29	18.74 ± 5.1
II	75	34.1 ± 0.4	7.24 ± 0.23	21.83 ± 1.6 ^b	15.78 ± 1.6

Note. Results expressed as mean ± SEM unless otherwise indicated.

^aRevised ASRM endometriosis score (12).

^b $p < 0.001$ vs. Group I.

which resection, ablation, or a combined approach was performed was also similar between the groups. As would be expected based on the construct of the study, there was a significant difference between the groups with regard to the interval between surgery and oocyte aspiration.

The results of gonadotropin stimulation and cycle outcome are presented in Table II. There were no differences between the groups with regards to response to controlled ovarian hyperstimulation. The stimulation protocols employed, dose and duration of gonadotropins required and mean number of oocytes obtained were similar between the groups. In addition, mean fertilization rates, number of embryos transferred, and implantation rates per embryo transfer procedure were also similar. There were no statistical differences in the percentages of patients undergoing ICSI, assisted hatching or blastocyst transfer. Extremely encouraging ongoing pregnancy and overall implantation rates which were not significantly different between the groups were noted (Fig. 1).

In an effort to address the effect of the interval between most recent surgical treatment of endometriosis and oocyte aspiration and implantation, regression analysis was performed. No significant correlation was noted. Likewise, no relationship between the extent of endometriosis as measured by the revised American Society for Reproductive Medicine (ASRM) staging system and implantation was appreciated (12) (Table III).

DISCUSSION

In this investigation we have demonstrated that the time interval between surgical management of endometriosis and oocyte aspiration has no significant effect on IVF-ET cycle outcome in the absence of significant or persistent ovarian disease. No impact with regards to the response to controlled ovarian hyperstimulation, ongoing pregnancy rates or implantation rates was appreciated. Surgical procedures for endometriosis performed shortly before cycle initiation in the absence of large (>3 cm) ovarian endometriomas do not appear to enhance pregnancy rates.

The primary therapeutic approach for the asymptomatic patient with endometriosis-related infertility has traditionally been surgical. Two well-designed meta-analyses have both demonstrated consistently higher pregnancy rates with surgical treatment in comparison to either no treatment or medical suppression (7,13). Only two prospective randomized trials have addressed the effect of surgical management of minimal–mild endometriosis on fertility in comparison to untreated controls. In an elegantly designed multicenter trial, Marcoux *et al.* reported that ongoing pregnancy rates were significantly higher and pregnancies were achieved more rapidly in patients undergoing surgical ablation of endometriosis as opposed to those undergoing diagnostic laparoscopy alone (5). A smaller but similarly designed prospective randomized trial of infertile women with minimal–mild

Table II. Cycle Outcome

Group	Total gonadotropin dose (75 IU ampules)	COH duration ^a (Days)	Oocytes retrieved	Fertilization (%)	Embryos transferred	IR/ET ^b (%)
I	41.1 ± 3.4	10.0 ± 0.2	17.8 ± 2.2	62.8 ± 5.4	3.3 ± 0.2	34.6 ± 7.9
II	43.5 ± 1.8	10.0 ± 0.1	17.1 ± 1.1	59.8 ± 2.3	3.1 ± 0.1	36.2 ± 4.3

Note. Results expressed as mean ± SEM.

^aCOH = Controlled ovarian hyperstimulation.

^bIR/ET = Implantation rate per embryo transfer procedure.

Fig. 1. Ongoing pregnancy and group implantation rates in patients undergoing surgical resection of endometriosis ≤ 6 months prior (Group I) and >6 –60 months (Group II) prior to oocyte aspiration. There were no significant differences between the groups.

endometriosis revealed no difference in pregnancy rates between the groups after 1 year (14). In an analysis of a series of studies reporting outcomes from conservative laparoscopic surgery for infertility in patients with stages III and IV endometriosis, Candiani noted an overall cumulative pregnancy rate of 47.6% (6). However, monthly fecundity rates were noted to range from 2.1 to 3.3%.

Nevertheless, the majority of spontaneous pregnancies after surgical therapy appear to occur within the first six postoperative months (5,14). Thus, in the current investigation, a 6-month interval was felt to be a reasonable break point to differentiate a potential beneficial effect of surgery on IVF-ET outcome. Regression analysis demonstrated that there was no relationship between the interval between surgery and oocyte aspiration and implantation rates throughout the 5-year evaluation period (Table III). It is unlikely that surgical ablation would have had a significant

benefit on cycle outcome in Group II patients given that the mean $\pm$ SEM interval between surgery and oocyte aspiration was 21.83 ± 1.6 months. One of the weaknesses of the current trial is its retrospective design which can provide a source of confounding variables and selection bias. In addition, the presence of a control group of endometriosis patients undergoing IVF-ET with a diagnosis of endometriosis who had not undergone surgical ablation would have further enhanced the investigation. However, this would have required that patients undergo diagnostic laparoscopy alone. In light of the previously reported beneficial effects of surgical treatment of endometriosis on spontaneous conception, it would appear that there would have been little additional information gained by the addition of such a group. Needless to say, the current investigation was not designed to evaluate the effect of surgical intervention upon spontaneous conception, but rather to evaluate the effect of surgical intervention on IVF-ET cycle outcome.

Patients without anatomic distortion who suffer from endometriosis-related infertility purportedly benefit from surgical therapy. A host of investigators have demonstrated that the pathogenesis of infertility in patients with minimal or mild endometriosis may stem from alterations in the peritoneal environment creating a "hostile" environment for successful gamete interaction and early embryo development (3,4). Employing a murine IVF model, Miller *et al.* demonstrated that laser laparoscopy appeared to reverse the inhibitory effects of serum from infertile women with endometriosis on both fertilization and early embryonic development rates (8). These results have not been confirmed and the mechanism of action of this postsurgical effect remains somewhat speculative. Surrey and Hill demonstrated in a prospective randomized trial that although CO₂ laser vaporization at the time of gamete intrafallopian transfer (GIFT) produced no deleterious effects on cycle outcome, subsequent posttreatment spontaneous pregnancy rates were higher than in those endometriosis patients who failed to conceive from GIFT performed without surgical treatment of the disease (15).

It is certainly logical that patients with more advanced stages of endometriosis with distorted anatomy and pelvic adhesions would most benefit from surgical reconstruction if pelvic anatomy can be restored to normal and postoperative adhesions minimized. Although this approach would conceivably benefit spontaneous conception rates, the benefit of pelvic reconstruction on IVF-ET outcome

Table III. Regression Analyses

Variables	Statistics	
	<i>r</i>	<i>p</i>
Surgery–oocyte aspiration interval (months) vs. implantation	–0.127	ns
Endometriosis score (12) vs. implantation	–0.097	ns

in the absence of extensive ovarian disease would be more difficult to explain. The lack of beneficial effect appreciated from surgical management of endometriosis demonstrated in the current investigation was not, however, related to the extent of the disease (Table III). This confirms findings of previous investigators who have demonstrated that ongoing pregnancy rates were not affected by disease stage in endometriosis patients with endometriosis undergoing IVF-ET (1,2,16). However, a recent study reported compromised birth rates in patients with moderate and severe endometriosis (6.7%) in comparison to controls with tubal factor infertility (16.6%) (17). The results of this trial may be tempered by the fact that comparisons were not made to those from patients with less severe disease and delivery rates were somewhat compromised in both groups. Pal *et al.* reported that although fertilization rates were lower in patients with Stage III/IV in comparison to Stage I/II endometriosis undergoing IVF-ET, implantation, clinical pregnancy, and miscarriage rates were similar between the groups (18).

It is important to note that patients with ovarian endometriotic cysts >3 cm in mean diameter present at the time of cycle initiation were excluded from the investigation. The incidence of those who had previously undergone resection of such cysts was similar between the groups (Group I: 26.3% vs. Group II: 21.1%). It is logical to assume that such persistent cysts might have an adverse impact on response to controlled ovarian hyperstimulation. Al-Azeni *et al.* described a decrease in ovarian response requiring the use of higher gonadotropin doses in patients with endometriomas (19). Yanushpolsky and colleagues have reported a higher incidence of pregnancy loss and an adverse effect on number of oocytes retrieved and embryo quality in this group of patients (20). Others have reported no impact (1). Unfortunately, none of these investigators have correlated endometrioma size with outcome.

In an effort to avoid a second confounding variable, patients who had received long-term GnRH agonist therapy within the 6 months prior to IVF cycle initiation were also excluded. In a prospective randomized multicenter trial, Surrey *et al.* have recently demonstrated that a 3-month course of a long-acting GnRH agonist administered to infertile endometriosis patients immediately prior to IVF-ET resulted in significantly higher ongoing pregnancy rates than those undergoing standard stimulation protocols (21). These findings have been confirmed by others (22–25). This may be due to a benefi-

cial effect of these agents on endometrial markers of implantation (26). The inclusion of such patients in the current investigation could have skewed the results.

In the current retrospective analysis, we have demonstrated that in infertile patients with endometriosis, surgical ablation or resection performed in the 6 months prior to IVF-ET did not have a beneficial effect on cycle outcome in the absence of large endometriomas. Neither the time nor the extent of disease had an impact on implantation. Clearly, these data do not suggest that there would be an advantage to delaying the onset of an indicated IVF cycle after surgical therapy for endometriosis, but neither would there be a benefit in repeating laparoscopy closer to the time of the onset of a cycle in the absence of significant ovarian disease. Any potential benefit derived from such surgery in enhancing spontaneous conception may be overcome by the inherently higher rates of ongoing pregnancy and implantation associated with IVF-ET. The performance of a prospective randomized trial which would necessitate the inclusion of a control group of endometriosis patients undergoing diagnostic laparoscopy alone as a control to confirm these findings would be most beneficial.

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