

Unilateral versus bilateral adnexal disease in stage III and stage IV endometriosis does not affect pregnancy outcome after operative laparoscopy

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Abstract To study the effect of unilateral versus bilateral adnexal involvement on the pregnancy rate after operative laparoscopy. Historic cohort study. A total of 143 patients with advanced stages of endometriosis (stage III and IV) who underwent operative laparoscopy for infertility treatment were categorized into those with unilateral versus bilateral adnexal disease. Forty-three patients had primarily unilateral (group 1) and 100 had bilateral disease (group 2). Follow-up was up to 2 years. There was no significant difference between group 1 and group 2 with respect to

pregnancy rates (28% vs 31%), delivery rates (21% vs 23%), miscarriage rates (25% vs 13%), and ectopic rates (0% vs 13%). Cumulative conception rates after up to 24 cycles of natural intercourse and up to three IUI cycles were 59% and 49% for group 1 and group 2, respectively. Operative laparoscopy for advanced stages of endometriosis appears to be an effective treatment modality for establishing a pregnancy in infertile patients. Pregnancy and delivery rates are not different in patients with unilateral or bilateral adnexal involvement.

Keywords Advanced endometriosis · Pregnancy outcome · Laparoscopic surgery · Unilateral · Bilateral

Support: None

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Introduction

Although stage III and IV endometriosis suggest advanced disease, endometrial implants and adhesions are frequently not symmetrically distributed in the pelvis [1] allowing for the possibility that one adnexa may be relatively free of mechanical factors of infertility. The fact that one adnexa may have less disease may positively influence the pregnancy rate reported as a result of surgical treatment of advanced endometriosis. That is to say, the pregnancy occurs as a result of ovulation/tubal ovum pickup from the side with less adnexal pathology. However, in such cases the resulting pregnancy may be due to the effect of ablation of endometrial implant, as in patients with minimal or mild endometriosis [2]. If such a hypothesis is true, the pregnancy rate should be much less in patients with bilateral adnexal involvement. To examine this hypothesis, we therefore studied the effect of unilateral versus bilateral adnexal involvement on the pregnancy rate after operative laparos-

copy for infertile patients with advanced endometriosis. We also studied the pregnancy and delivery rates in these two groups and in the total population after different infertility treatment methods were used.

Materials and methods

This is a retrospective historical cohort study conducted after obtaining approval by the local institutional research board of Wayne State University. The study was conducted at a private infertility center (IVF Michigan). All patients with advanced stages of endometriosis (stage III and IV) who underwent operative laparoscopy for infertility treatment between April 1993 and December 2003 were studied. Endometriosis was staged at the time of surgery according to the revised American Fertility Society classification (rAFS) [3]. Patients whose husbands had severe male factor (count less than 10 million/ml, and/or motility less than 20%, and/or very poor morphology) and patients with cycle day 3 FSH level higher than 12 mIU/ml were excluded. Patients with past history of pelvic inflammatory disease (PID), history of sexually transmitted disease and/or positive *Chlamydia trachomatis* serology (IgG/IgM) were excluded. A total of 143 consecutive patients who satisfied the criteria were included in our study. Patients were characterized into those with unilateral versus bilateral adnexal disease. Adnexal disease was defined as mechanical distortion of the adnexa due to the presence of deep-seated endometrioma(s) and/or adhesions of the ovary to the ovarian fossa and/or extensive peritubal and/or peri-ovarian adhesions. Unilateral disease was defined as similar anatomical distortions mechanically affecting only one adnexa. Superficial implants of the opposite adnexa, in the absence of adhesions or endometrioma(s), did not disqualify a patient as having primarily unilateral disease. Patients designated as being in the bilateral group had significant ovarian and/or tubal pathology distorting both adnexae. Using these criteria, 43 patients had primarily unilateral and 100 had bilateral disease.

Surgery was performed by the same surgeon (M. I. A.) under similar operative setting in all patients. The same surgical techniques and procedures were applied in all patients. When suspicious spots of endometriosis were found anywhere in the pelvis, in the majority of cases, argon beam coagulator (Birtcher Medical System, Irvine, CA, USA) was used to ablate the spots seen. If endometriosis was found on the pelvic sidewall near the ureter, on the bladder or bowels, CO₂ laser (Sharplan Lasers, Inc., Allendale, NJ, USA) vaporization was performed. Salpingo-ovariolysis was performed using blunt dissection of the ovary from the pelvic sidewall, and scissors and/or monopolar diathermy needle tip to excise scar tissue from

the tubes and ovaries. If an endometrioma of more than 1 cm was found, excision of the cyst wall was done and reconstruction of the ovarian cortex was performed with one or two interrupted sutures using 3-0 Vicryl. If an endometrioma of less than 1 cm was found, it was opened, evacuated, and the lining was ablated with the argon beam coagulator. If fimbrial phimosis or hydrosalpinges were found, fimbrioplasty or salpingostomy was performed, respectively. Starting in 1999, temporary ovarian suspension was performed when laparoscopic surgery was performed for advanced endometriosis in an attempt to reduce the risk of recurrence of adhesions between ovarian fossa and ovaries [4].

Following surgery, Clomid was given to patients with anovulatory disorder. Intrauterine insemination (IUI) after controlled ovarian hyperstimulation (COH) was performed if male factor or ovulatory disorder resistant to Clomid (not responding by ovulation) was present, or after 6 months of natural intercourse. Some patients opted to start infertility intervention in the form of COH+IUI or in vitro fertilization and embryo transfer (IVF-ET) directly after surgery.

During IUI, ovarian hyperstimulation was achieved using mid-luteal gonadotropin-releasing hormone agonist (GnRH-a) pituitary down regulation followed by gonadotropin injections starting on the second or third day of the menstrual cycle. Ten thousand units of human chorionic gonadotropin (hCG) was given when the dominant follicle reached a diameter of 17 mm, and IUI was performed 42 h later. For IVF/ET, controlled ovarian hyperstimulation was applied according to a long GnRH-a pituitary down regulation protocol. In the first few years of this series, traditional IVF was performed. However, intracytoplasmic sperm injection (ICSI) was performed in all patients in the last 5 years of this series.

In all patients studied, we calculated endometriosis scores in five categories: cul-de-sac, peritoneum, ovaries, tubal, and grand total. After excluding patients who conceived with IVF-ET (in whom pregnancy is not secondary to surgery), we compared these scores in patients who conceived and those who failed to conceive in each group and in the total population studied. In addition, after excluding 31 patients who conceived after IVF/ET, the data were then analyzed with respect to the effect of the underlying etiology.

Pregnancy was confirmed by vaginal ultrasonography and delivery verified by phone follow-up. Patients were followed until delivery if pregnant, or for a period of 24 months following surgery if not pregnant. Data were expressed as means±SD. Student's *t*-test, chi square analysis, and Kruskal–Wallis one way anova analysis were used for statistical analysis where appropriate. Cumulative conception rate (CCR) was calculated using life table analysis. To determine if there was any statistical signifi-

cance in CCR between the two groups, further survival analysis was performed; the Kaplan–Meier survival analysis log rank test was used.

Results

The mean age at laparoscopy was 31.8 ± 4.5 years. The mean duration of infertility was 3.4 ± 2.7 years. Table 1 shows the demographic data of both groups. The two groups did not differ significantly in age and duration of infertility, although the latter approached significance with a tendency for longer duration of infertility in the unilateral group. A significantly higher number of patients had primary infertility in the unilateral group. In addition, there were no significant differences in the underlying etiologies of infertility between the two groups. Of the patients studied, 78 patients (55%) had primary infertility. Forty-three patients (30.1%) had endometriosis as their sole cause of infertility and 100 patients (69.9%) had other infertility factors (e.g., mild male factor or ovulatory disorder) in addition to endometriosis.

Tables 2, 3 and 4 illustrate pregnancy outcome after spontaneous conception, conception after IUI+COH, and combination of the two methods, respectively. There was no significant difference in the pregnancy rates between the unilateral versus bilateral groups after spontaneous (19% vs 21%), IUI+COH (40% vs 53%), and combined methods (28% vs 31%), respectively. In addition, there was no significant difference in delivery rates between the two groups after spontaneous (14% vs 15%), IUI+COH (30% vs 42%), or combined (21% and 23%) conceptions, respectively. Furthermore, there was no significant difference in miscarriage rates and ectopic pregnancy rates between the two groups, according to the method used to achieve conception. The overall conception rate, delivery rate, miscarriage rate, and ectopic pregnancy rate were 20%, 15%, 17%, and 10% with spontaneous conception; 42%, 38%, 14%, and 7% after COH+IUI; and 30%, 22%, 16% and 9% after combined methods, respectively. There were no significant differences in the CCR between

unilateral versus bilateral groups after spontaneous conception (53% vs 43%), IUI+COH (47% vs 81%), or combined (59% vs 49%), respectively.

Some of the patients elected to proceed with IVF/ET shortly after surgery when they were told of the extent of their endometriosis. Others tried spontaneously and/or IUI+COH for a few cycles before they decided to proceed with IVF/ET. Fifty-one patients underwent 75 cycles of IVF/ET during the study period. There was no significant difference between the two groups in the pregnancy rate per patient (67% vs 58%), the delivery rate per patient (56% vs 49%), miscarriage rate (8% vs 11%), and ectopic pregnancy rate (8% vs 5%), respectively.

Of the 51 patients who underwent IVF/ET, 31 patients conceived. The pregnancy and delivery rates per patient were 61% and 51%, respectively, while the miscarriage and ectopic pregnancy rates were 10% and 7%, respectively.

After excluding 31 patients who conceived after IVF-ET, the data were then analyzed and the pregnancy outcome after combined methods (spontaneous conception and IUI+COH) were calculated. The pregnancy rate and delivery rate were 39% and 29% in the unilateral group, 38% and 28% in the bilateral group and 38% and 29% in the total population, respectively. We also compared the pregnancy rates between the two groups according to the underlying etiology. There was no significant difference in the pregnancy rate in relation to the underlying etiology between the two groups. Above 50% of patients achieved pregnancy and approximately 40% delivered in both groups when all possible infertility interventions were used. When all possible infertility treatment methods were used, cumulative conception rate and cumulative delivery rate after 24 months were 66% and 62% for group 1, 69% and 68% for group 2, and 76% and 67% for the total population studied, respectively.

We compared endometriosis scores in patients who conceived and those who failed to conceive in the two groups and in the total population after excluding patients who conceived with IVF-ET. There was no significant difference in the endometriosis score in the unilateral group, while in both the bilateral group and in the total

Table 1 Demographic data

	Unilateral	Bilateral	<i>P</i> value	Total
Number of patients	43	100		143
Age	32.0 ± 4.7	31.8 ± 4.5	NS	31.8 ± 4.5
Duration of infertility	4.0 ± 3.0	3.1 ± 2.5	0.052	3.4 ± 2.7
Type of infertility				
Primary infertility	31 (72%)	47 (47%)	<0.01	78 (54.5%)
Etiology of infertility				
Endometriosis alone	8 (18.6%)	35 (35%)	NS	43 (30.1%)
Endometriosis plus other infertility factors	35 (81.4%)	65 (65%)	NS	100 (69.9%)

Table 2 Pregnancy outcome after spontaneous conception

	Number of patients	Pregnant (%)	Delivered (%)	Miscarried (%)	Ectopic (%)	CCR ^a
Unilateral	43	8 (19)	6 (14)	2 (25)	0 (0)	53%
Bilateral	100	21 (21)	15 (15)	3 (14)	3 (14)	43%
Total	143	29 (20)	21 (15)	5 (17)	3 (10)	46%

^a Cumulative conception rate up to 24 months after surgery

population there was significantly lower ovarian scores ($P=0.007$ and $P=0.001$, respectively) and grand total scores ($P=0.001$ and $P=0.001$, respectively) in the conceived versus non-conceived. No difference was detected in the tubal scores among the unilateral group, bilateral group, and the total population.

Discussion

Although endometriosis is present in 25–50% of infertile women, [5, 6] the majority of these patients have early stages of endometriosis. Since mechanical factors interfering with ovum pick up play an important role in the mechanisms of infertility in patients with advanced stages of endometriosis, the majority of these patients require either surgical correction or IVF/ET to achieve pregnancy. Many studies reported very low cumulative conception rate (CCR) in patients with advanced stages of endometriosis without surgical treatment [7–10] compared to CCR in patients with early stages of endometriosis [11–13]. Olive and colleagues reported no pregnancies among women with severe endometriosis with expectant management, as compared to 52% with mild endometriosis and expectant management during a 25-month follow-up [9]. In addition, several reports suggested good CCR after surgical treatment of advanced endometriosis both by laparotomy and laparoscopy [14–16]. Other reports suggested no difference in the pregnancy outcome whether laparotomy or laparoscopy was utilized. [14, 17]

Now, for more than a decade, laparoscopy has become the gold standard of conservative surgical treatment of infertility patients with endometriosis [14–16]. It allows the surgeon to reach a diagnosis and allows him/her to proceed

with treatment of endometriosis and/or adhesions at the time of surgery. Improvement in fecundity rate and CCR have been reported after laparoscopic surgical treatment for infertile patients with both early [2] and advanced stages of endometriosis [14, –18]. However, none of these studies evaluated the effect of unilateral versus bilateral adnexal involvement on the chances of achieving pregnancy postoperatively.

Our data indicate that surgical treatment for advanced endometriosis is effective even when bilateral adnexal involvement is present. Our results, with a CCR of 53% after spontaneous cycles, are similar to the results reported by other investigators, which suggested that approximately 50% of patients conceived after laparoscopic surgery for advanced endometriosis [19]. In addition, our results are in agreement with others that laparoscopic surgery can improve pregnancy rates in patients with advanced disease [18, 20]. In a recent report by Littman et al., of the 19 patients with advanced stage of endometriosis, eight conceived (seven spontaneously and one after Clomid/IUI) [42%] [21]. In our study, when both spontaneous and IUI+COH methods of conception were used, we were able to achieve a CCR of 59%, 49%, and 52% for the unilateral group, bilateral group, and the total population studied, respectively. However, our data also suggest that when ovarian endometriosis scoring is high in bilateral disease, the chances are less favorable. It may partly explain the difference in pregnancy rate after laparoscopic surgical corrections of advanced endometriosis in various reports. Busacca et al. reported a cumulative conception rate of 51% and 17% after operative laparoscopy for stage III and IV endometriosis, respectively [22]. Similar to our data, this report suggests the more advanced (higher scores), the less likely the chances of pregnancy. Similarly, Adamson et al.

Table 3 Pregnancy outcome after IUI+COH

	Number of patients	Number of cycles	Number pregnant per cycle (%)	Number pregnant per patient (%)	Number delivered per cycle (%)	Number delivered per patient (%)	Number miscarried (%)	Number ectopic (%)	CCR ^a
Unilateral	10	19	4 (21)	4 (40)	3 (16)	3 (30)	1 (25)	0 (0)	47%
Bilateral	19	32	10 (31)	10 (53)	8 (25)	8 (42)	1 (10)	1 (10)	81%
Total	29	51	14 (28)	14 (42)	11 (22)	11 (38)	2 (14)	1 (7)	73%

^a Cumulative conception rate up to 24 months after surgery

Table 4 Pregnancy outcome after combined methods (spontaneous conception and IUI+COH)

	Number of patients	Number pregnant per patient (%)	Number delivered per patient (%)	Number miscarried (%)	Number ectopic (%)	CCR ^a
Unilateral	43	12 (28)	9 (21)	3 (25)	0 (0)	59%
Bilateral	100	31 (31)	23 (23)	4 (13)	4 (13)	49%
Total	143	43 (30)	32 (22)	7 (16)	4 (9)	52%

^a Cumulative conception rate up to 24 months after surgery

reported that extensive endometriosis with higher ASRM score (>71), was associated with reduced pregnancy rates [23]. Other reports suggested that older patients and those with stage IV did not conceive as often [19].

In one recent study, Maruyama [24] found that cumulative rates of pregnancy after laparoscopic treatment of endometriosis are about 35%. Maruyama found a significantly lower cumulative pregnancy rate in a group of patients with bilateral tubal adhesions compared with those patients with unilateral or no tubal adhesions. However, he did not find a difference in the pregnancy outcomes of those patients with minimal/mild endometriosis versus moderate/severe endometriosis if the endometriosis did not include tubal disease. This suggests that endometrial implants resulting in mechanical factors interfering with tubal function may have a stronger impact on pregnancy outcome than the extent of endometrial disease as reflected merely in staging. This may explain the relative success of laparoscopic correction of mechanical factors in even those patients with severe stages of endometriosis. In our study, when we evaluated the effect of tubal involvement, we could not find any significant difference between patients who conceived and those who failed to conceive. Such findings were maintained in both unilateral and bilateral groups and also in the total population studied. We attribute such findings to the fact that we excluded from this study all patients who had history of PID and/or those who had positive serology for *Chlamydia trachomatis*. Since endometriosis is a disease of the peritoneum, surgical correction of any tubal pathology in our patients may have a better prognosis than in patients with PID.

Our data also suggest that IUI+COH can enhance pregnancy chances after laparoscopic surgery for advanced endometriosis. In our study, approximately one-third of patients with advanced endometriosis were able to conceive within 2 years after operative laparoscopy as a result of spontaneous trials and/or IUI+COH. Other reports suggested similar results when IUI+COH was used after operative laparoscopy for early and advanced endometriosis [25–27]. Therefore, it could be offered for two to three cycles either immediately following surgery or after three to four failed cycles of spontaneous trials.

Our data suggest consistent excellent results of IVF-ET after operative laparoscopy. Therefore, our result is in favor of the IVF-ET procedure after surgery for endometriosis. IVF-ET should be considered after operative laparoscopy whenever there is marked bilateral ovarian involvement and/or failure of conception spontaneously, or after a few trials of IUI+COH. In addition, it should be considered from the outset in patients with additional infertility factors; e.g., male factor, advanced female age, and prolonged duration of infertility. Recently, Littman et al. reported eight IVF pregnancies (five in patients with stage III or IV) in patients with endometriosis after operative laparoscopy who had two failed IVF cycles on average. However, the literature is not conclusive on this issue [28–30]. It is worth of note that ICSI is being utilized more frequently in these patients in view of reports of decreased fertilization rate after traditional IVF/ET [29, 31, 32]. Some reports suggested that ICSI can overcome apparent defects in oocytes derived from endometriosis patients [33].

However, our study has some limitations including its retrospective nature, the heterogenous group of patients studied with the fact that only 30% of the patients had endometriosis as their only cause of infertility and the fact that, following surgery, the patients were not carried forward in a similar manner. On the other hand, this study was carried out by one surgeon at one unit and therefore, represents consistent management over the period of the study. In addition, it is extremely difficult to answer the question posed in this study by limiting the data to only those with the single diagnosis of endometriosis. Furthermore, the fact that spontaneous pregnancy rate is similar in both groups is very suggestive that laparoscopic surgical treatment is as effective in the presence of bilateral adnexal involvement as in unilateral adnexal disease irrespective of the presence of additional infertility factors.

In conclusion, the data in our study suggest that conservative laparoscopic surgery for advanced stages of endometriosis appears to be an effective treatment modality in patients with both unilateral and bilateral adnexal involvement. However, a large prospective study is needed to confirm our findings. In addition, IUI+COH may enhance chances of conception in patients with advanced endometri-

osis after operative laparoscopy. However, as expected, the more advanced the disease, the lesser the likelihood of pregnancy after surgical correction. Such patients should be counseled to consider other opportunities including proceeding with IVF-ET, which can achieve excellent results.

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