Comparison of Fecundity after Second Laparotomy for Endometriosis to in Vitro Fertilization and Embryo Transfer

Sopon Cheewadhanaraks MD*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University*

Objective : *To study the prognosis for conception subsequent to a second conservative laparotomy for infertile patients with moderate and severe endometriosis, compared with the reproductive outcome of one cycle of in vitro fertilization and embryo transfer (IVF-ET).*

Material and Method : *From January 1990 to February 2000, 190 infertile patients had initial conservative laparotomy for pelvic endometriosis at a university hospital. All of these patients had moderate or severe endometriosis. After the failure of the initial operation to restore fertility, 32 patients requested the second operation while 24 patients underwent one cycle of IVF-ET. The cumulative pregnancy rate after the second operation was compared with the clinical pregnancy rate after one cycle of IVF-ET.*

Result : *The cumulative pregnancy rate following the reoperation was 20.5% within 1 year with no additional increase in 2 and 3 years of follow up. The clinical pregnancy rate per stimulation of one cycle of IVF-ET was 12.5%. There was no statistically significant difference (P = 0.54).*

Conclusion : *Despite a trend toward a higher cumulative pregnancy rate following the second conservative laparotomy, there was no statistically significant difference, when compared with one cycle of IVF-ET in moderate and severe endometriosis-associated infertile patients who had not conceived after the initial operation.*

Keywords : *Endometriosis, Infertility, In vitro fertilization and embryo transfer, Surgery*

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When moderate or severe endometriosis causes anatomic distortion, tubal obstruction and pelvic adhesions or ovarian endometriomas, surgery is usually the treatment of choice for endometriosis-associated infertility because it allows the opportunity to restore normal anatomy[1]. Conservative surgery for endometriosis may be performed via laparotomy or laparoscopy. The relative value of laparoscopy in comparison to lapartomy is debatable[2]. After the first conservative laparotomy for moderate to severe endometriosis, without hormonal treatment, the cumulative probability of pregnancy within 2 years was 28%-62%[3-5]. The treatment for the patients who remained infertile may be a second conservative surgery or IVF-ET. Information concerning the second operation and IVF-ET, especially the success rate, is mandatory in counseling these patients. Therefore, the present study aimed to clarify the prognosis for conception subsequent to a second conservative procedure, compared with the clinical pregnancy rate of one cycle (procedure) of IVF-ET in moderate to severe endometriosis-associated infertile patients.

Correspondence to : Cheewadhanaraks S, Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand. Phone & Fax: 0-7442-9617, E-mail: csophon@medicine.psu. ac.th

Material and Method

From January 1990 to February 2000, 190 infertile patients had conservative operations for pelvic endometriosis. No preoperative hormonal treatment was administered. The surgical technique. After the exploratory laparotomy was performed, the endometrioma, adhered to the posterior leaf of the broad ligament, was carefully displaced from this site before resection was attempted. The ovarian cortical surface was reapproximated as closely as possible. The adhesion of the distal fallopian tube was freed. Areas of endometriosis on the posterior surface of the uterus and cul-de-sac or on the anterior surface of the rectosigmoid were excised as completely as possible. Unilateral salpingo-oophorectomy was performed

when it was impossible to preserve the ovary[6]. During the operative procedure the pelvis was irrigated with Lactated Ringer's solution. At the conclusion of the surgical procedure, 500 ml. of Dextran-70 or Gelofusine in normal saline solution was placed in the peritoneal cavity. Histopathologic diagnosis of endometriosis was made in all patients. No postoperative hormonal drug was administered. Clomiphene citrate was given when there was anovulatory problem. Cervicitis were treated with antibiotics. The patients were advised to become pregnant by regular natural sexual intercourse.

The indications for repeat conservative surgery were recurrent endometrioma and/or no conception after the primary operation for at least one year. The surgical technique was the same as described above, without preoperative or postoperative hormonal drugs. After the second operation the patient was managed with the same policy as after the first one.

Thirty-three patients who underwent the initial operation failed to return to the clinic for at least one year; the outpatient and inpatient charts of the 157 patients who returned for postoperative follow up were studied. Of the 157 patients studied, 101 underwent only the single conservative procedure for endometriosis during the period in which they were evaluated, while 56 patients requested the second operation or IVF-ET. After counseling, without randomization, the patients were free to choose either the second operation or IVF-ET.

Thirty-two of 56 patients required the second operation. However, only 30 patients returned to the clinic for at least one year of follow up.

Twenty-four of 56 patients underwent IVF-ET. The female patients were stimulated with a long protocol, starting with nasal gonadotrophin releasing hormone agonist (GnRHa; Suprefact, Hoechst) on day 23-25 of the preceding cycle. When pelvic ultrasonography revealed adequate ovarian suppression, human menopausal gonadotrophin (hMG; Pergonal, Serono and Humegon, Organon) was administered intramuscularly along with GnRHa starting at 225 IU per day. The growth of the follicles was monitored with pelvic ultrasonography starting five days later and then every other day. Dosage of hMG was adjusted according to the growth of the follicles. When at least two leading follicles had reached 18 mm in diameter or more, 10,000 IU of human chorionic gonadotrophin (hCG; Pregnyl, Organon) was injected intramuscularly. The oocyte retrieval was performed 34-35 hours later transvaginally with ultrasound guidance. In the laboratory room, the oocyte-cumulus complexes were washed and transferred to the Earle culture media drops supplemented with 10% maternal serum, covered with mineral oil (embryo tested, Sigma), in the CO_2 incubator (5% CO_2 in air). Sperm preparation was performed with the discontinuous Percoll gradient (40%/90%) centrifugation method. After 3-4 hours of incubation, the oocyte-cumulus complexes were inseminated at the concentration of 100,000 spermatozoa/ml.

The two-pronuclei zygotes with second polar body were selected and transferred to the Earle culture medium with 15% maternal serum under the mineral oil layer. Forty-eight hours after oocyte retrieval, the three best embryos were selected and transferred back into the uterine cavity transcervically using the Earle culture medium supplemented with 50% maternal serum. The rest of the embryos were cryopreserved for later use. The luteal phase was supported with progesterone and continued until 10 weeks of pregnancy for the positive cases[7].

Demographic and infertility characteristics analyzed included age at operation, duration of infertility, previous pregnancy and semen analysis. Severity of endometriosis was graded according to revised American Fertility Society[8]. Adnexal involvement with disease sufficient to warrant resection was also noted. Pathologic processes that coexisted with endometriosis and that were treated at operation were recorded. Obstetric history was recorded for both preoperative and postoperative periods. Cumulative pregnancy rate was calculated.

Statistical analysis: the life-table method was used to calculate the cumulative pregnancy rate and the data obtained were compared by Wilcoxon test. Since each patient had only one IVF-ET treatment, the clinical pregnancy rate per stimulation of one cycle of IVF-ET was used as pregnancy events, supposed to occur in the first month of the 12 months follow up, in calculating the cumulative pregnancy rate at 1 year. When appropriate, the patient characteristics of the study groups were compared using Student's t-test, and chi-square analysis. Statistical significance was defined as $P < .05$.

Results

Patient clinical characteristics at the time of initial conservative operation of all the patients and the two study groups i.e. the repeat operation and the IVF-ET are presented in Table 1. The percentage of

Table 1. Patient clinical characteristics at the time of the first operation.

	All (n = 157)	Repeat Operation (n = 30)	IVF-ET (n = 24)	*P* value
Female age (mean SD, year)	32.0 4.3	29.9 3.9	32.7 3.9	ns
Duration of infertility (mean SD, year)	3.7 2.9	2.6 1.9	3.6 2.4	ns
Primary infertility (%)	79.6	80.0	83.3	ns
Normal semen analysis (%)	82.8	83.3	75.0	ns
Stage of endometriosis				
Moderate (%)	29.9	26.7	29.2	ns
Severe (%)	77.1	73.3	70.8	
Unilateral salpingo-oophorectomy (%)	21.0	23.3	25.0	ns
Coexisting pathology (leiomyomas) (%)	12.7	13.3	16.7	ns

- between the repeat operation and IVF-ET groups
ns - not significant

primary infertility and normal semen analysis did not vary significantly between the two groups. Stage of endometriosis was either moderate or severe; and there was no significant difference between the groups. Another indicator of severity of endometriosis is adnexal damage sufficient to indicate its resection. Requirement for unilateral salpingo-oophorectomy did not vary significantly between the groups. Leiomyomas were the only coexisting pathologic condition, and were similarly distributed between the groups of patients.

There was no significant difference in female age and duration of infertility, at the time of the second conservative operation or IVF-ET, between the group of repeat operation and IVF-ET. (Table 2)

Results of IVF-ET cycles are described in Table 3. From 24 stimulation cycles, 2 cycles were cancelled due to poor response. Twenty-two oocyte retrieval were performed and resulted in 221 oocytes collected. Sixty-nine percent of these oocytes could be fertilized normally and 84% of the zygotes resulted in cleaving embryos. The mean number of fresh and thawed transferred embryos were 4.50. Three pregnancies were diagnosed and all are singletons. No pregnancy occurred when thawed embryos were transferred. This resulted in a 12.5% clinical pregnancy rate per stimulation

Cumulative pregnancy rate is presented in Table 4. There was no statistically significant difference between clinical pregnancy rate per stimulation of one cycle of IVF-ET and cumulative pregnancy rate at 1 year after the second conservative laparotomy. In contrast to the initial operation, no pregnancy occurred during the second and third year of follow up after the repeat operation.

Pregnancy outcomes are described in Table 5. No miscarriage was noted in the IVF-ET group. The miscarriage rate in the second operation group

Table 2. Female age and duration of infertility recorded at the time of second operation or IVF-ET

	Repeat Operation (n = 30)	IVF-ET (n = 24)	*P* value
Age (mean SD, year)	33.0 4.3	34.2 3.8	ns
Duration of infertility (mean SD, year)	5.6 2.9	5.1 2.4	ns

ns - not significant

Table 3. Results of IVF-ET treatment cycles

Stimulation cycle (n)	24
Oocyte retrieval cycle (n)	22
Collected oocytes per retrieval (mean SD)	10.0 5.4
Total collected oocytes (n)	221
Fertilization rate (%)	69.2
Cleavage rate (%)	84.9
Transferrred embryos per retrieval (mean SD)	4.5 3.3
Clinical pregnancy rate per retrieval (%)	13.6
Clinical pregnancy rate per stimulation (%)	12.5

Table 4. The cumulative number of pregnancies and cumulative pregnancy rate (%)

	All (n = 157)	Repeat operation (n = 30)	IVF-ET (n = 24)	*P* value
1 yr.	40 (28.7%)	6 (20.5%)	3 (12.5%)	0.54
2 yr.	53 (42.4%)	6 (20.5%)	Na	na
3 yr.	55 (45.8%)	6 (20.5%)	Na	na

- between cumulative pregnancy rate of the repeat operation and IVF-ET groups.
na - not available

Table 5. Pregnancy outcomes

	Single operation	Repeat operation	IVF-ET
Total conceptions	55	6	3
Term pregnancy	49	5	3
Miscarriage	6	1	0

was 16.6%. However, the pregnancies are too few to be statistically useful.

Discussion

The benefits of surgical treatment in minimal and mild endometriosis for promoting fertility is controversial. However, moderate and severe disease is associated with anatomic distortion, and surgical restoration of the tubo-ovarian anatomy is essential for improving the rate of conception.

In the present study, after the initial conservative surgery for endometriosis-associated infertility, the cumulative pregnancy rate of 28.7%, 42.4% and 45.8% within 1, 2 and 3 years respectively, occurred by natural sexual intercourses. Garcia and David[3] reported the results of conservative laparotomy, without hormonal treatment; for severe stage of endometriosis, the cumulative pregnancy rate was 28.5% within 2 years and for moderate stage was 36.8% within 2 years and 5 months. Adamson et al[4] studied the moderate to severe endometriosis patients who underwent the conservative laparotomy, without preoperative or postoperative hormone, and found that the cumulative pregnancy rates were 23.8%, 36.7% and 44.4% within 1, 2 and 3 years respectively. The cumulative pregnancy rate of these two studies and the present study were comparable. Crosignani et al[5] studied the outcome of laparoscopy compared with laparotomy in conservative surgical treatment for severe endometriosis, without preoperative medical therapy. They found a 24-month cumulative pregnancy rate of 62.7% after laparotomy. This very high cumulative pregnancy rate may be explained by their criteria excluding any women with other causes of infertility.

With regard to the presented data relating to the second conservative laparotomy, the cumulative pregnancy rate was 20.5% within 1 year, with no additional increase in 2 and 3 years of follow up. Wheeler and Malinak[9] found that 7 of 15 (47%) patients conceived within 18 months after a second conservative laparotomy. However, 31% of their patients had mild severity of endometriosis at the initial operation. Candiani et al[10] evaluated the recovery of infertility in 28 women undergoing repetitive conservative laparotomy for recurrent endometriosis. Eleven patients presented other infertility factors. The cumulative pregnancy rate at 27 months was 30.7%. Pagidas et al[11] reported the cumulative pregnancy rate after reoperation, using laparoscopic techniques, for moderate or severe endometriosis-related infertility after 3, 7 and 9 months was 5.9%, 18.1% and 24.4% respectively. All of their patients had undergone a complete infertility evaluation and any women with additional factors for infertility were excluded from the study. Busacca et al[12] compared laparotomy with laparoscopy for conservative treatment for recurrent endometriosis. All male partners had two semen analyses to exclude dyspermia. They found cumulative pregnancy rates at 24 months of 45% in the laparotomy and 54% in the laparoscopic group. No statistically significant difference was observed. From the data of these studies and the present study, the cumulative pregnancy rate after a second conservative surgery for endometriosis-related infertility varied considerably, depending on the severity of disease and other infertility factors.

It is very controversial whether or not patients with endometriosis might have IVF-ET compromised cycles[13-28] However, a recent meta-analysis[29] of the published literature on IVF-ET showed that women with endometriosis have decreased pregnancy rates. The presented clinical pregnancy rate per stimulation of one cycle of IVF-ET in patients with moderate and severe endometriosis-related infertility, who failed to conceive after the initial conservative operation, was 12.5%. It is slightly lower than the pregnancy rate in patients with tubal factor in IVF-ET programme, which was 17.5% per stimulation (7 pregnancies in 40 cycles).

In the treatment of moderate and severe endometriosis after failure of initial surgery to restore fertility, IVF-ET or second conservative surgery may be offered to patients as the treatment of choice. Information concerning IVF-ET and second conservative surgery is mandatory in counseling these patients. Pagidas et al[11] found that the cumulative pregnancy rate after one cycle of IVF-ET was higher than with reoperation, 33.3% versus 24.4%, respectively, although no statistical significance could be obtained. In contrast, the presented cumulative pregnancy rate after one cycle of IVF-ET was lower than those undergoing a second operative procedure, 12.5% versus 20.5%. However, there was no statistically significant difference.

Finally, patients with recurrent endometrioma should be counseled to have a reoperation, because the presence of endometriomas at the time of oocyte retrieval is associated with increased rates of early pregnancy losses[30].

In conclusion, after failure of initial conservative laparotomy for moderate to severe endometriosis-associated infertility, patients should be informed

that despite a trend toward a higher cumulative pregnancy rate following the second conservative laparotomy, there was no statistically significant difference in the success rate, when compared with one cycle of IVF-ET.

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เปรียบเทียบผลการตั้งครรภ์หลังการผ่าตัดทางหน้าท้องครั้งที่สองเพื่อรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่กับการปฏิสนธินอกร่างกายและการย้ายฝากตัวอ่อน

โสภณ ชีวะธนรักษ์

วัตถุประสงค์ *: เพื่อศึกษาอัตราการตั้งครรภ์หลังการผ่าตัดอนุรักษ์แบบเปิดหน้าท้องครั้งที่สองในผู้ป่วยที่มีบุตรยากที่มีภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ความรุนแรงปานกลาง และมาก เปรียบเทียบกับอัตราการตั้งครรภ์หลังการทำปฏิสนธินอกร่างกาย และการย้ายฝากตัวอ่อนหนึ่งรอบระดู*

วัสดุและวิธีการ *: ตั้งแต่เดือนมกราคม พ.ศ.2533 จนถึงเดือนกุมภาพันธ์ พ.ศ.2543 มีผู้ป่วยมีบุตรยาก จำนวน 190 ราย ได้รับการผ่าตัดอนุรักษ์แบบเปิดหน้าท้องครั้งแรก เพื่อรักษาภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ในอุ้งเชิงกรานที่โรงพยาบาลของมหาวิทยาลัย ผู้ป่วยทั้งหมดมีความรุนแรงของพยาธิสภาพขั้นปานกลาง หรือ มาก เมื่อปรากฏว่าผู้ป่วยไม่ตั้งครรภ์หลังการผ่าตัดครั้งแรก ผู้ป่วยจำนวน 32 ราย ขอรับการผ่าตัดครั้งที่สองในขณะที่ 24 ราย ขอรับการทำปฏิสนธินอกร่างกาย และการย้ายฝากตัวอ่อนหนึ่งรอบระดู ได้นำอัตราการตั้งครรภ์สะสมหลังการผ่าตัดครั้งที่สองมาเปรียบเทียบกับอัตราการตั้งครรภ์ที่ตรวจพบทางคลินิกหลังการทำปฏิสนธินอกร่างกายและการย้ายฝากตัวอ่อนหนึ่งรอบ*

ผลการศึกษา *: อัตราการตั้งครรภ์สะสมหลังการผ่าตัดครั้งที่สองพบว่ามี 20.5% ภายใน 1 ปี และไม่พบว่ามีการตั้งครรภ์อีกในปีที่ 2 และ 3 ของการติดตาม อัตราการตั้งครรภ์ที่ตรวจพบทางคลินิกหลังการทำปฏิสนธินอก ร่างกายและการย้ายฝากตัวอ่อนหนึ่งรอบการกระตุ้นไข่ คิดเป็น 12.5% ไม่พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (P = 0.54)*

สรุป *: แม้ว่าอัตราการตั้งครรภ์สะสมหลังการผ่าตัดอนุรักษ์แบบเปิดหน้าท้องครั้งที่สองจะสูงกว่าอัตราการตั้งครรภ์หลังการทำปฏิสนธินอกร่างกาย และการย้ายฝากตัวอ่อนหนึ่งรอบในผู้ป่วยมีบุตรยากที่ตรวจพบภาวะเยื่อบุโพรงมดลูกเจริญผิดที่ความรุนแรงปานกลาง หรือ มาก แต่อย่างไรก็ตามไม่พบว่าแตกต่างกันอย่างมีนัยสำคัญทางสถิติ*