

# Recurrent endometriosis and IVF: is it still an enigma?

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## Summary

The recurrence of endometriosis varies between 6% and 67%. If the patient is infertile and has recurrent endometriosis, she could be managed by repeat surgery or assisted reproduction. Given the increasing number of patients with recurrent endometriosis applying for IVF procedure, the aim of this study was to compare IVF outcome in patients who underwent one or more surgeries for endometriosis for the purpose of offering proper counseling to the infertile patients. The authors compared IVF outcome measures between 50 patients once operated for endometriosis with no signs of the disease at the time of IVF procedure, 29 patients also once operated for endometriosis with signs of the disease at the time of IVF procedure, and 47 patients more than once operated for endometriosis. Each group was also compared with a control group of 157 patients with tubal factor infertility. Outcome measures included number of follicles, number of oocytes, mean number of ampoules of gonadotropins, cumulative pregnancy, and live birth rates. The rate of cancelled cycles was higher in all three groups of patients with endometriosis compared to the control group, and in addition, significantly higher in patients who underwent two or more endometriosis surgeries. The same applied for the number of oocytes retrieved by puncture and the number of the obtained embryos. The rate of implantation, clinical and multifetal pregnancies, as well as the birth rate per embryo transfer was significantly lower in patients who underwent endometriosis surgery two or more times, compared to all other groups of patients. When it comes to recurrent endometriosis, repeat surgery worsens the IVF outcome and therefore should be avoided. Except in cases of patients experiencing unbearable pain and suspicious ovarian mass findings, a patient with recurrent endometriosis should be immediately included in the IVF procedure without repetitive surgery.

**Key words:** Recurrent endometriosis; In vitro fertilization; Tubal factor infertility.

## Introduction

Endometriosis is one of the most puzzling gynecologic diseases. It affects 2-10% of women in general population and 20-50% of women who are investigated for infertility. The link between infertility and endometriosis has long been established; although further theories about the association of these two entities are still being proposed [1]. Surgery remains the mainstay in the diagnosis and management of endometriosis [2]. The methods of assisted reproduction, primarily in vitro fertilization, have been adopted as a common procedure for achieving pregnancy in patients with endometriosis and associated problem of infertility. The most common approach for treatment of patients with infertility, depending on a patient's age, is surgery and ART if spontaneous conception does not occur within a certain period of time after surgery [3].

Various studies have shown significantly different data on the recurrence of endometriosis. Depending on the criteria taken into account, the overall recurrence rate is between 6% to 67%. However, it is still uncertain which of the various reasons is more predictive for recurrence of endometriosis; thus the issue remains disputable. Whether a treatment will be effective is determined by the resorption of all residual visible lesions and elimination of microscopic implants. The recurrence may be caused by regrowth of residual lesions or may arise from the development of

de novo cells. It is of great importance to establish the risk factors associated with the recurrence in order to identify subgroups at high risk and thus control the disease more effectively [4].

An interesting situation arises when patients with endometriosis fail to conceive after the first surgical procedure and have recurrent endometriosis. These infertile patients could be managed by repeat surgery or assisted reproduction. The main question is what is the best chance for achieving pregnancy for patients with recurrent endometriosis.

Given the increasing number of patients with recurrent endometriosis applying for IVF procedure, the aim of this study was to compare IVF outcome in patients who underwent one or more surgeries for endometriosis for the purpose of offering a proper counseling to infertile patients affected by recurrent endometriosis.

## Materials and Methods

A total of 235 first-attempt IVF cycles performed in two IVF units (IVF Unit in Clinic for Gynaecology and Obstetrics Clinical Center of Nis, Serbia and IVF Unit in Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina Novisad, Serbia) were prospectively analyzed in a three-year period (December 2012-December 2015). A total of 126 women were enrolled consecutively and diagnosed with endometriosis. All patients with endometriosis had previously undergone laparoscopy; 62 patients

were diagnosed with minimal and mild endometriosis (American Society for Reproductive Medicine stage I/II) and 64 with moderate and severe endometriosis (American Society for Reproductive Medicine stage III/IV). Seventy-nine patients had only one surgery whereas 47 patients underwent more than one surgery. There were 50 patients with no signs of endometriosis at the time of IVF procedure and 29 patients with recurrent endometriosis after the first surgery. All patients with endometriosis were treated with three to six cycles of GnRH analogues after laparoscopy and prior to IVF. The control group consisted of 157 women with laparoscopically diagnosed tubal factor infertility and without any evidence of endometriosis, who underwent IVF treatment during the same time period. Sample size estimation was performed to determine the number of women per group sufficient to detect a true odds ratio (OR) of 2.5. Depending on the women's age, the antral follicle count and the basal (day 3) follicle stimulating hormone (FSH), the long GnRH-agonist downregulation protocol (dipherelin 0,1 mg) and the short GnRH-agonist or GnRH antagonist protocol (cetrotide) were used. Ovulation stimulations were conducted with daily subcutaneous injections of individual starting doses of rFSH (folitropin alpha or folitropin beta or human menopausal gonadotropin (hMG) at appropriate doses (50-450 IU). Ovarian response to gonadotropins was monitored by transvaginal ultrasound and serum estradiol (E2) measurement every second day beginning from day 7. Ovulation was triggered by injecting 10,000 IU hCG at the moment of the leading follicle reaching the size of 18 mm with appropriate serum E2 levels. Thirty-six hours after administration of hCG, transvaginal ultrasound-guided oocyte aspiration was performed under local anaesthesia. After cultivation, embryo transfer was performed three to five days after oocytes aspiration. All patients received luteal phase support for two weeks. Clinical pregnancy was defined as the visualization of gestational sac at ultrasound examination and biochemical pregnancy was defined as detection of  $\beta$ -hCG levels in serum but no signs of pregnancy by ultrasound. Data are expressed as the mean  $\pm$  standard deviation or as percentages. Statistical comparisons among groups were performed using the Fisher exact test,  $\chi^2$  test, Wilcoxon's test or Student's *t*-test.

## Results

Table 1 shows the characteristics of patients and controlled ovarian hyperstimulation in all three groups of patients with endometriosis (operated once with no signs of endometriosis at the time of entering the IVF treatment, operated once with recurrent endometriosis at the time of inclusion in IVF, and those operated two or more times), and patients with tubal factor infertility. Table 2 shows IVF laboratory parameters as well as the IVF outcome in the aforementioned groups of patients.

The rate of cancelled cycles was higher in all three groups of patients with endometriosis compared to the control group, and in addition, significantly higher in patients who underwent two or more endometriosis surgeries. The same applies for the number of oocytes retrieved by puncture and the number of the obtained embryos. The rate of implantation, clinical and multifetal pregnancies, as well as the birth rate per embryo transfer was significantly lower in patients who underwent endometriosis surgery two or more times, compared to all other groups of patients. Among the patients who had one surgery, with or without

recurrent endometriosis at the time of entering the IVF treatment, there were no differences in any of the examined parameters aside from the miscarriage rate, which was higher in patients with recurrent endometriosis compared to all other examined groups of women.

## Discussion

A certain number of patients operated for endometriosis will experience recurrent endometriosis, whereas infertile patients who wish to achieve pregnancy may also face a dilemma of whether or not to undergo a repeated surgery.

The recurrence of endometriosis in the present study was 60%, which is consistent with literature data [4]. Many studies have examined the effect of reoperation on reducing chronic pelvic pain and dysmenorrhea [5, 6].

The rate of pain recurrence following repeat conservative surgery for recurrent endometriosis-associated pain ranges between 20 and 40%. Presacral neurectomy may be a good choice for alleviating midline pain. Nonetheless, so far there have not been any studies conducted to assess the performance of this procedure among patients with recurrence of the disease. Repeat conservative surgery for recurrent endometriosis pain is equally efficient as well as limited, as primary surgery [7]. On the other hand, there is little information regarding the benefit of repeated surgery for the reproductive outcome. A study by Vercellini *et al.* showed a significantly higher rate of spontaneous pregnancies after the first surgical treatment of endometriosis (40%), compared to the rate after repeat surgery (22%) [8].

A study by Berland *et al.* revealed a conception rate of 26% among women undergoing repetitive surgery for recurrent endometriosis associated with infertility, compared to a reported overall crude pregnancy rate of 41% after a primary procedure [7]. The two studies, however, have not examined only the pregnancies achieved by IVF, but the overall pregnancy rate.

Two studies compared the pregnancy rate after repeat endometriosis surgery and IVF performed after the primary surgery for endometriosis. According to a study conducted by Pagidas *et al.*, in 18 women who underwent second surgery for moderate or severe endometriosis (stage III or IV) the observed nine-month cumulative pregnancy rate was 24.4%, whereas the pregnancy rate was 33.3% and 69.6% in 23 women who underwent one or two IVF cycles, respectively [9]. In their study Cheewadhanaraks *et al.* [10] reported a 12-month cumulative pregnancy rate of 20.5% in 32 patients treated by repeat laparotomy and a clinical pregnancy rate of 12.5% in 24 patients who had one IVF cycle. Based on the OR of 1.70 (95% CI 0.67-4.32), surgery is not recommended as a method superior to IVF [10]. However, these studies also observed the cumulative pregnancy rate after repeat surgery for endometriosis. The only study similar to ours is the study by Fedele *et al.* from 2006 [11]. They examined ovarian reserve after the primary and re-

Table 1. — Characteristics of patients and control ovarian hyperstimulation. A: Patients once operated for endometriosis without signs and symptoms of endometriosis at the time of IVF procedure. B: Patients once operated for endometriosis with recurrent endometriosis at the time of IVF procedure C: Patients with more than one surgery for endometriosis.

	A	B	C	Tubal infertility	C vs. A, B
N. of patients	50	29	47	157	
Age (years)	32.8 ± 3.2	33.7 ± 2.7	35.7 ± 3.9*	33.2 ± 3.2	$p < 0.05$
BMI (kg/m <sup>2</sup> )	26.2 ± 7.2	24.3 ± 5.8	26.8 ± 5.9	25.7 ± 6.1	NS
Duration of infertility (years)	7.4 ± 4.5	7.09 ± 3.1	9.8 ± 5.8*	7.7 ± 4.3	$p < 0.05$
Primary infertility (%)	79.8***	81.2***	80.9***	60.1	NS
FSH day 3 (IU/ml)	7.8 ± 2.8	7.5 ± 2.6	9.6 ± 3.5****	6.9 ± 2.5	$p < 0.001$
N. of gonadotropin ampoules	34.6 ± 11.2**	36.4 ± 12.5**	42.6 ± 24.4****	27.2 ± 9.5	$p < 0.001$
Duration of stimulation (days)	9.56 ± 1.9	8.83 ± 1.2	11.8 ± 2.4*	9.22 ± 1.8	$p < 0.05$
E2 day 7 (pg/ml)	712 ± 522*	670 ± 494*	439 ± 319**	822 ± 678	$p < 0.005$
N. of follicles >16 mm	6.3 ± 3.4*	6.03 ± 2.9*	3.32 ± 3.1***	7.9 ± 6.4	$p < 0.01$

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.005$ , \*\*\*\* $p < 0.001$ ; all refer to control group (tubal infertility).

Table 2. — IVF laboratory parameters and IVF outcome. A: Patients once operated for endometriosis without signs and symptoms of endometriosis at the time of IVF procedure. B: Patients once operated for endometriosis with recurrent endometriosis at the time of IVF procedure. C: Patients with more than one surgery for endometriosis.

	A	B	C	Tubal infertility	B vs. A	C vs. A, B
Cancelled cycles (%)	13.7**	14.2**	27.2****	5.7	NS	$p < 0.05$
N. of oocytes	5.9 ± 3.1*	5.6 ± 2.9*	3.9 ± 2.25***	7.6 ± 6.1	NS	$p < 0.01$
Fertilization (%)	53.7	53.6	47.2	54.2	NS	NS
N. of embryos	3 ± 2.5*	2.9 ± 2.2*	1.8 ± 1.2***	4 ± 2.8	NS	$p < 0.01$
Implantation (%)	22.37	24.8	13.8**	23.11	NS	$p < 0.01$
N. of pregnancies per ET (%)	47.9	46.4	25.1**	46.9	NS	$p < 0.01$
N. of miscarriages (%)	22.2	31.2*	24.2	19.8	$p < 0.05$	$p < 0.05$ (B vs. C)
Multifetal pregnancies (%)	39.4	35.4	21.2**	40	NS	$P < 0.05$
N. of deliveries per ET (%)	28.1	27.1	18.1*	27.5	NS	$P < 0.05$

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.005$ , \*\*\*\* $p < 0.001$ ; all refer to control group (tubal infertility).

peat surgery and found a much larger number of patients with basal FSH levels higher than 14 IU/l among patients who underwent undergone more than one endometriosis surgery. Furthermore, their study is the only one that compared the outcome of IVF after the first-line and repeat surgery (50% vs. 32.2%).

To the best of the present authors' knowledge, this is the only study that compared the IVF outcomes among patients who underwent one surgical treatment for endometriosis, patients with recurrent endometriosis after the primary surgery who entered the IVF treatment, and those who underwent two or more endometriosis surgeries. In this study, patients that underwent two or more surgical interventions for endometriosis had a significantly worse ovarian response to controlled hyperstimulation as well as worse IVF outcomes, compared to all other groups of patients. In addition, the patients who underwent repetitive surgical interventions for endometriosis had significantly higher FSH levels, compared to the patients who underwent one endometriosis surgery, as well as to those with tubal factor infertility. It appears that a repeat surgery after the ovarian response has been already quantitatively reduced by the previous surgery and a subsequent disease which per se af-

fects healthy ovarian tissue, significantly impairs ovarian reserve which is definitely reflected by a poor IVF outcome.

Adamson stressed the importance of providing patients with a proper explanation of the benefits and costs of various treatment alternatives. Taking the age and infertility duration into consideration, it is essential to design an individualized treatment plan. The pros of surgery include histological confirmation of the disease and notable pain relief, whereas the cons involve higher treatment cost, morbidity, and a longer period needed for conceiving [12].

A larger number of prospective randomized studies on the recurrence of endometriosis are needed, due to the fact that the routine use of laparoscopy for endometriosis in combination with the tendency of the disease to relapse has changed the clinical scenario in reference institutions, where patients with recurrent endometriotic lesions represent a real challenge in daily clinical practice. It is well known that repeat surgery for endometriosis is more technically demanding and potentially more risky than the primary surgery. In order to adequately counsel patients, these risks should be taken into account along with the postoperative results.

## Conclusion

When it comes to recurrent endometriosis, repeat surgery worsens the IVF outcome and therefore should be avoided. Except in cases of patients experiencing unbearable pain and suspicious ovarian mass findings, a patient with recurrent endometriosis should be immediately included in the IVF procedure without repetitive surgery.

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