

In vitro fertilization outcome in women with endometriosis & previous ovarian surgery

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Background & objectives: Women with endometriosis often need *in vitro* fertilization (IVF) to conceive. There are conflicting data on the results of IVF in patients with endometriosis. This study was undertaken to elucidate the influence of endometriosis on IVF outcome to give the best counselling for infertile patient with this problem.

Methods: The outcome measures in 78 patients with surgically confirmed endometriosis were compared with 157 patients with tubal factor infertility, all of whom have undergone IVF. The groups were matched for age and follicle stimulating hormone (FSH) levels. Outcome measures included number of follicles, number of oocytes, peak oestradiol (E2) concentrations and mean number of ampoules of gonadotropins. Cumulative pregnancy, miscarriage and live birth rates were calculated in both the groups.

Results: Higher cancellation rates, higher total gonadotropin requirements, lower peak E2 levels and lower oocyte yield were found in women with endometriosis and previous surgery compared with those with tubal factor infertility. However, no differences were found in fertilization, implantation, pregnancy, miscarriage, multiple births and delivery rates between the endometriosis and tubal factor infertility groups.

Interpretation & conclusions: The present findings showed that women with endometriosis and previous surgery responded less well to gonadotropins during ovarian stimulation and hence the cost of treatment to achieve pregnancy was higher in this group compared with those with tubal factor infertility. However, the outcome of IVF treatment in patients with endometriosis was as good as in women with tubal factor infertility.

Key words Endometriosis - gonadotropins - infertility - *in vitro* fertilization - pregnancy

Endometriosis affects 2-10 per cent of women in general population and 20-50 per cent of women who are investigated for infertility¹. Despite extensive studies, the exact mechanism by which endometriosis

cause infertility is not clearly understood. *In vitro* fertilization and embryo transfer (IVF-ET) has become a common method to help women with endometriosis-associated infertility. Using IVF-ET it is possible

to bypass the suspected disturbed functions which affect the natural cycles by endometriosis such as altered folliculogenesis, ovulatory dysfunction, oocyte maturation, cleavage of embryo and implantation^{2,3}.

The results of different studies on whether the outcome of IVF-ET is as good in women with endometriosis as in patients with other causes of infertility, are controversial. Some investigators have reported poor IVF outcome in women with endometriosis related infertility^{4,5}, while others reported high success rates comparable to those in women with tubal factor infertility^{6,7}. The present study was undertaken to analyze the results of IVF-ET and to elucidate the influence of endometriosis on IVF outcome in women with endometriosis who have undergone laparoscopy compared with those women with tubal factor infertility to give the best counselling for infertile patients with endometriosis.

Material & Methods

A total of 235 first-attempt IVF cycles performed in two IVF units outcome (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 three years period (December 2009-December 2012). The study protocol was approved by the Ethics Committee of both IVF units and the study was conducted after obtaining informed written consent of all patients. A total of 78 women were enrolled consecutively and diagnosed with endometriosis. All patients with endometriosis have previously undergone laparoscopy; 40 patients were diagnosed with minimal and mild endometriosis (American Society for Reproductive Medicine stage I/II) and 38 with moderate and severe endometriosis (American Society for Reproductive Medicine stage III/IV)⁸. Of these 78 women, 68 had undergone only one and 12 more than one surgical procedures. In all patients with ovarian endometriosis the "stripping" technique was used to excise endometriomas and the diagnosis was histologically confirmed. All patients with endometriosis were treated with 3-6 cycles of gonadotropin releasing hormone (GnRH) analogues after laparoscopy and prior to IVF. The control group consisted of 157 women who underwent IVF treatment during the same time period, with laparoscopically diagnosed tubal factor infertility and without any evidence of endometriosis.

Sample size estimation was performed to determine the number of women per group sufficient to detect a true odds ratio (OR) of 2.5. With a power of 80 per cent, type 1 error of 5 per cent, and 0.20 probability of exposure in controls, it was calculated that at least 69 subjects (ORs = 2.5) were required in the study group and at least 138 subject in the control group.

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, Ipsen Pharma Biotech, France), the short GnRH-agonist or GnRH antagonist protocol (Cetrotide, Serono Pharma, Switzerland) were used. Ovulation stimulations were conducted with daily subcutaneous injections of individual starting doses of rFSH (Foliotropin alpha- Gonal F, Serono Pharma, Switzerland or Foliotropin beta- Puregon, Organon, or human menopausal gonadotropin (hMG) (Menopur, Feriing, Germany) at appropriate doses (50-450IU). Ovarian response to gonadotropins was monitored by transvaginal ultrasound and serum estradiol (E2) measurement (Abcam, USA) every second day from day 7. Ovulation was triggered by injecting 10000IU hCG when the leading follicle reached 18 mm with appropriate serum E2 levels. Thirty six hours after administration of human chorionic gonadotropin (hCG), transvaginal ultrasound-guided oocyte aspiration was performed under local anaesthesia. After cultivation, embryo transfer was performed 3 to 5 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 β -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, χ^2 test, Wilcoxon's test or Student's t test as appropriate.

Results

Patients characteristics and ovarian stimulation parameters are shown in Table I. Women with endometriosis required more ampoules of gonadotropins and attained lower serum E2 levels on day 7. The number of follicles ≥ 16 mm on the day of hCG administration was significantly ($P < 0.05$) lower compared to tubal factor patients group. Primary infertility and OHSS rates were significantly ($P < 0.05$) lower in women in the endometriosis group.

Table I. Patient characteristics and controlled ovarian hyperstimulation parameters

	Endometriosis	Tubal factor in infertility
No. of patients	78	157
Age (yr)	33.7 ± 3.3	33.2 ± 3.2
BMI (kg/m ²)	25.5 ± 5.1	25.7 ± 6.1
Primary infertility (%)	80.7*	60.1
Smoke (>5 cigarettes/day)	31%	34%
FSH d3 (IU/ml)	7.6 ± 2.9	6.9 ± 2.5
Gonadotropins (%)		
rFSH	64.7	63.5%
hMG	35.3	36.5%
Mean no. of ampoules of gonadotropins	35.3 ± 16.7**	27.2 ± 9.5
Mean days of gonadotropins	9.19 ± 1.8	9.22 ± 1.8
E2 day 7 (pg/ml)	711.2 ± 56.6*	822 ± 67.8
No. of follicles ≥ 16 mm on day of hCG	6.1 ± 4.9*	7.9 ± 6.4
OHSS (%)	1.28*	6.2
<i>P</i> *<0.05, **<0.01 compared with total factor infertility group; FSH, follicle stimulating hormone; rFSH, recombinant FSH; hMG, human menopausal gonadotropins; E2, estradiol; BMI, body mass index; OHSS, ovarian hyperstimulation syndrome Data are expressed as mean ± SD where appropriate		

IVF laboratory parameters are presented in Table II. Cycle cancellation rate was significantly ($P<0.01$) higher for women in the endometriosis group compared with control group. Also, the total number of oocytes retrieved and total number of embryos were significantly lower in these endometriosis group. No significant differences were found between the groups with regard to the fertilization rate or percentage of blastocysts. A similar number of embryos were transferred in both the groups.

Implantation rates, clinical pregnancy rates and live birth rates were comparable between the two groups. No significant differences were found in the miscarriage rate and multifetal pregnancy rate between the endometriosis and tubal factors infertility groups of patients (Table III).

Discussion

There is a lack of consensus among studies as to whether ovarian response is adequate or suboptimal in patients with ovarian endometriosis. Some studies have reported impaired ovarian responsiveness to ovarian stimulation in patients with endometriosis^{8,9} and others reported lack of adverse effect^{10,11}. We found a detrimental relationship between endometriosis and ovarian response during controlled ovarian

hyperstimulation in IVF. Despite having similar FSH levels on day 3 in women with endometriosis with previous ovarian surgery compared with those with tubal factor infertility, women with endometriosis required significantly higher dosages of gonadotropins, achieved lower peak E2 levels and yielded fewer oocytes. Women with endometriosis had also higher cycle cancellation rates. These findings suggested that the ovarian responsiveness was damaged after the presence and excision of ovarian endometriomas. There are currently insufficient data to clarify whether this endometrioma-related damage to ovarian responsiveness precedes or follows surgery. Elucidation of this point is important as it would impact on the decision of whether to operate on women with endometriosis who are selected for IVF. At present, there appears to be evidence supporting both an endometrioma-related injury^{12,13} and surgery-mediated damage^{14,15}.

There is also a lack of consensus in the reported literature on IVF success in patients with endometriosis. In a meta-analysis of 22 studies, Barnhart *et al*¹⁶ reported that the odds of pregnancy in patients with endometriosis undergoing IVF/ET was 50 per cent compared to women with tubal factor infertility. The findings of Witsenburg *et al*¹⁷ are in contrast to the previous one. Based on the Centers for Disease Control

Table II. IVF laboratory parameters in women with endometriosis compared with women with tubal factor infertility

	Endometriosis (n=78)	Tubal factor infertility (n=157)
Mean no.of oocytes retrieved	5.6 ± 4.3*	7.6 ± 6.1
Fertilization rate (%)	53.6	54.2
Total number of embryos	2.9 ± 2.1*	4 ± 2.8
Blastocyst (%)	13.8	19.9
Mean no. of transfered embryos	2.31 ± 1.41	2.58 ± 0.9
Cycle cancellation rate (%)	16.67*	5.7
-poor ovarian response	53.8	22
-no oocytes retrieved by aspiration	23	34
-no fertilization	23	29
-OHSS	0	15

*P**<0.05 **<0.01 compared with tubal factor infertility group
Data are expressed as mean ± SD where appropriate: OHSS, cycle canceled due to ovarian hyperstimulation syndrome

Table III. IVF outcomes (%) in women with endometriosis and tubal factor infertility

	Endometriosis	Tubal factor
Implantation rate (%)	22.04	23.4
Cumulative pregnancy rate per ET	44.6	46.9
Biochemical pregnancies per ET	3.62	4.7
Clinical pregnancies per ET	39.8	40.5
Ectopic pregnancies	1.2	1.7
Miscarriages	23.5	19.8
Multifoetal pregnancies	34.5	40
Live birth rate per ET	26.15	27.52
ET, embryo transfer		

(CDC) data, similar pregnancy and live birth rates have been reported when comparing couples with diagnosis of tubal factor infertility, ovulatory dysfunction, endometriosis, male factor and unexplained infertility¹⁷. We found no adverse outcome of endometriosis (after ovarian surgery) on fertilization and implantation rate in the present study. Although fewer embryos were available for transfer, as a consequence of fewer yielded

oocytes, the same number of embryos were transferred. Moreover, in contrast to other groups of women with diminished ovarian reserve, implantation rate, pregnancy rates and miscarriage rates were similar in the two groups. There were no significant differences in the live birth rates between women with endometriosis and those with tubal factor infertility.

These contrasting results can be explain by several hypotheses. First of all, it seems that reduced ovarian responsiveness is related to quantitative rather than qualitative damage after surgery for ovarian endometriosis. Secondly, ovarian endometriomas are monolateral in 72-81 per cent of cases¹⁸. Bilateral disease was present in 13 per cent of patients in our study. The contralateral intact ovary may adequately compensate for the reduced function of the affected one. Third, all patients in our study were treated with GnRH agonists for 3 to 6 month after the surgery and prior to IVF. Data from Cochrane collaboration reports that long-term administration of GnRH agonists prior to IVF in women with endometriosis increases the odds of clinical pregnancies by at least four-fold and live-birth rate by tree-fold¹⁹. The improvement in the live birth and clinical pregnancy rate in patients receiving GnRH analogues may be due to an improvement in the quality of oocytes (and hence the embryos) or due to an improvement in the uterine receptivity leading to better implantation and diminished loss of very early pregnancies. Many studies have tried to give an answer by using oocyte donation (OD) programme²⁰⁻²². The overall conclusion, using the fact that women receiving oocytes from donors with endometriosis had reduced implantation rate and on the other hand, the women patients with and without endometriosis receiving oocyte from non endometriotic donor had the same implanatation rate, was that endometrial priming protocol with GnRH agonists used in OD cycles reestablished an adequate uterine cavity environment. One of the proposed mechanisms is that GnRH agonists restore the normal apoptotic rate (usually low in eutopic and ectopic endometrial cells from women with endometriosis)²³. There is a need for further research into the exact mechanism by which GnRH agonist improves pregnancy rates.

Inspite the fact that women with endometriosis require higher doses of gonadotropins for ovarian stimulation and hence the cost of treatment to achieve pregnancy is higher, the outcome of IVF treatment in women with endometriosis is as good as in women with tubal factor infertility.

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