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Original Research Article

A Prospective Cohort Study Evaluating Medical or Surgical Treatment of Endometriosis and Fertility

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Abstract:

Objectives: To evaluate the impact of medical and surgical endometriosis treatment on IVF reproductive outcomes in patients with primary infertility.

Material and Methods: The study, conducted over a three year period (2020-2023), included 51 patients with endometriosis associated primary infertility. Group I included patients treated for endometriosis before the IVF (subgroups A: surgical and pharmacological treatment and B: only surgical treatment). Group II included patients immediately subjected to IVF. Assessed outcomes were pregnancy rate (PR) per started cycle, fertilization rate (FR), implantation rate (IR) and live birth rate (LBR).

Results: Group IA included 17 patients, Group IB 17 and Group II 17 patients. FR and IR showed no significant differences between groups. PR was significantly higher in the Group I than Group II (49% vs 25%, p = 0.030). PR per started cycle was the highest in the Group IA and the lowest in the Group II (p = 0.040). LBR was significantly higher in whole Group I (p = 0.043) and subgroup IA (p = 0.020) than Group II. Group IA and IB did not differ regarding examined outcomes. Regression analysis showed that endometriosis pre-treatment method can impact both achieving pregnancy (p = 0.036) and having a live born child (p = 0.008) after IVF. The combined surgical and pharmacological endometriosis treatment, shorter infertility duration, lower EFI score, using long protocol with FSH+HMG gonadotropins increase the probability of successful IVF.

Conclusions: A combined surgical and pharmacological endometriosis treatment had a positive impact on IVF reproductive outcomes, both on pregnancy and on live birth rates.

Keywords: endometriosis; infertility; IVF; laparoscopic surgery; [follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P4) and anti-Mullerian hormone (AMH)].

Introduction

Compared to tubal factor, pregnancy rates (PR) after in vitro fertilization (IVF) are lower in endometriosis patients [1]. Therefore, IVF procedures are usually conducted after previous treatment of endometriosis [2]. Still, despite different approaches to the problem of infertility due to endometriosis, standard treatment protocols before IVF have not yet been defined. Some literature data indicate that prolonged administration of gonadotropin-releasing hormone (GnRH) agonists prior to IVF increases the pregnancy rates in endometriosis patients [3, 4]. Moreover, these patients can also have better reproductive outcomes.

Surgical approach presents a possible definitive treatment for endometriosis that at the same time enables avoiding side effects of prolonged medical treatment. Surgery as the treatment of minimal and mild endometriosis was shown in some studies to increase pregnancy rates both after natural conception and IVF during the first postoperative year [7, 8]. Nevertheless, other studies did not find any improvement in pregnancy rates when surgical therapy was compared to expectant management among women with endometriomas undergoing IVF [9]. Moreover, the main concern regarding surgery especially of larger ovarian lesions is surgery-related damage to ovarian reserve. Consequently, some

authors believe that surgery should be performed in case of advanced endometriosis with refractory pain or if malignancy cannot be ruled out [6].
Some studies showed that endometriosis surgical treatment, followed by a GnRH agonist therapy, might additionally increase pregnancy rates [9–11]. However, currently there is insufficient evidence of combined therapy (hormonal suppression before or after surgery) effects on symptoms relief, endometriosis recurrence and reproductive success.

Materials and Methods

This prospective cohort study was performed over a three-year period, selecting 51 patients with primary infertility caused by endometriosis to submit to IVF cycles. The study was approved by the Ethical Committee. All patients signed an informed consent before study enrollment.

Inclusion criteria were: age ≤ 4 years, primary infertility caused by endometriosis, the absence of other associated infertility factors, body mass index (BMI) ≤ 30 kg/m^2, regular cycles (22–35 days), adequate basal ovarian reserve (AMH ≥ 0.9 to 4.0 ng/mL; 3–15 antral follicles per ovary) [8, 12]. Exclusion criteria were: age > 40 years, BMI > 30 kg/m^2, secondary infertility, menstrual cycle disorders, associated infertility factors (male factor, endocrinological and ovulation disorders, genetic problems, uterine, cervical and tubal factor, unexplained infertility) and any other genital pathology. Patients enrolled in the study were divided into two groups based on the endometriosis treatment. The study Group I (GI) encompassed patients treated for endometriosis before the IVF while the Group II was the control with patients immediately subjected to the IVF cycles.

The selection criteria for the Group I were: having endometriomas > 3 cm and presence of moderate to severe endometriosis in the pelvis. Patients from the GI were additionally divided into two subgroups regarding additional medical therapy. Consequently, Group I subgroup A (GIA) included patients with previous combined surgical and medical treatment and Group I subgroup B (GIB) incorporated previously only surgically treated patients.

The Group II (GII) included patients with endometriosis that was not previously treated, but directly submitted to IVF (as a control group). The selection criteria for the Group II were: having endometriomas ≤ 3 cm and the presence of mild to moderate endometriosis in the pelvis.

General and medical data collection

Personal and medical history parameters were registered and analyzed for all patients: age, body mass index (BMI), infertility duration, standard laboratory and basal hormonal findings [follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P4) and anti-Mullerian hormone (AMH)]. All patients received a thorough gynecological and ultrasound assessment including uterine evaluation, antral follicles counting (AFC) and detecting presence, diameter and location of endometriosis.

Patients' diagnosis and treatment

Laparoscopy was performed for all patients of both groups for diagnosis of endometriosis (minimal tissue biopsy for histological confirmation) and/or surgical treatment. Guidelines of the American Society of Reproductive Medicine (ASRM) were used for diagnosing and staging of endometriosis. Upon laparoscopy the Endometriosis Fertility Index (EFI) and the ASRM endometriosis stage were determined [13, 14].

Surgical treatment for GI patients included ovarian cysts enucleating by capsule stripping technique with adhesiolysis where necessary and meticulous bipolar hemostasis for all endometriomas. Moreover, all visualized pelvic endometriosis foci were vaporized by bipolar clamp. Tissue samples were taken from the lesions for histopathological analysis. After surgical treatment of endometriosis, additional medical therapy for GIA group of patients included GnRH agonists every 28 days for six months.

The IVF procedure

The IVF procedure was scheduled up to six months after the completion of either surgical or combined treatment.

The controlled ovarian hyperstimulation (COH) was performed according to the three protocols: the long protocol with GnRH agonist, the short protocol with GnRH agonist and the short protocol with GnRH antagonist. Selection of the protocols depended on the patients age, EFI, FSH, E2, AMH serum levels and AFC. The long protocol implied the pituitary suppression with Diphereline® (Ferring Pharmaceuticals) 0.1 mg per day, during the seven days before the cycle onset and continuing daily to the end of ovulation stimulation. The short protocol implied the pituitary suppression with GnRH agonist, tryptorelin, in a dose of 0.1 mg per day from the 2nd or the 3rd cycle day and continuing daily to the end of ovulation stimulation. The short protocol with the GnRH antagonist implied the usage of the GnRH antagonist cetrorelix 0.25 mg per day from the 6th stimulation day and continuing daily to the end of stimulation. Ovarian stimulation started on the second or the third cycle day and it was conducted by giving daily subcutaneous injections of Rec-FSH and/or human menopausal gonadotropin (HMG) with starting dose of 300 IU. The ovarian stimulation was monitored by determination of serum E2 and LH levels and by transvaginal ultrasound monitoring of follicular growth and endometrium thickness every second

day from the sixth cycle day. When E2 values were above 400 pg/ml per follicle and there were at least two follicles > 18 mm, 5000 to 10000 IU of human chorionic gonadotropin (HCG) were administered. Follicular and oocyte aspiration were performed under transvaginal ultrasound control 34 to 36 hours after the administration of HCG. Ovarian response to stimulation was evaluated according to the number of retrieved oocytes (poor ≤ 4; adequate 5–15; excessive > 15 oocytes). Total number and quality of embryos was assessed by the embryologists and four embryo classes were defined as A, B, C and D (A class represents the highest embryo quality). In all cases fresh embryo-transfers of up to three quality embryos in day three were performed under the ultrasound control.

Follow-up and outcomes

The ultrasound check-up was performed two and six weeks after embryo transfer along with HCG testing. The primary outcome was achieving vital intrauterine clinical pregnancy, while pregnancy rate (PR) per started cycle, fertilization rate (FR — % fertilized oocytes transformed into two pronuclei) and implantation rate (IR — number of gestational sacs/numbers of transferred embryos) were secondary endpoints in all groups and subgroups. In case of successful pregnancy, women were regularly checked-up until delivery, according to current protocols. Finally, all adverse outcomes (miscarriages), pregnancy complications and live birth rate (LBR number of deliveries with a live born child per 100 embryo transfers) were recorded.

Observation chart

Table 1: Description of in vitro fertilization (IVF) cycles in relation to the endometriosis pre-treatment groups

Parameters		Total n = 51 patients	Group I n = 34 patients	Group II n = 17 patients	Between groups
Age ≤ 35		(55.8%)	(66.3%)	(36.9%)	0.004
Primary infertility > 3 years		(47.9%)	(34.8%)	(70.4%)	0.002
Body Mass Index ≤ 25		(86.3%)	(87.0%)	(85.2%)	0.680
EFI ≤ 7		(68.5%)	(63.0%)	(77.8%)	0.166
Endometriosis stage III–IV		(76.7%)	(91.3%)	(51.8%)	0.001
Presence of endometrioma		(68.5%)	(95.7%)	(22.2%)	0.001
Endometrioma > 3 cm		(58.9%)	(86.6%)	(14.8%)	0.001
ASRM score	< 16	(23.3%)	(8.7%)	(48.1%)	0.001
	16–40	(47.9%)	(52.2%)	(40.7%)	
	41–70	(21.9%)	(30.4%)	(7.4%)	
	≥ 71	(6.8%)	(8.7%)	(3.7%)	
Endometrioma localization	unilateral	(49.3%)	(73.9%)	(7.4%)	0.028
	bilateral	(19.2%)	(21.7%)	(14.8%)	
Protocol	Short + agonists	(26.0%)	(28.6%)	(21.4%)	0.442
	Short + antagonists	(40.3%)	(40.8%)	(39.3%	
	Long + agonists	(33.8%)	(30.6%)	(39.3%)	
Gonadotropins (IU)		2256.2 ± 776.4 (M = 2100.0)	2374.0 ± 831.4 (M = 2100.0)	2294.2 ± 680.2 (M = 2100.0)	0.388
Gonadotropins	FSH	(40.3%)	(36.7%)	(46.4%)	0.896
	HMG	(15.6%)	(8.2%)	(28.6%)	
	FSH + HMG	(44.2%)	(55.1%)	(25.0%)	
Number of aspirated oocytes		6.9 ± 5.5 (M = 5.5)	7.1 ± 4.9 (M = 5.00)	7.8 ± 6.2 (M = 7.00)	0.320
Ovarian response	poor	(44.2%)	(49.0%)	(35.7%)	0.676
	adequate	(48.1%)	(46.9%)	(50.0%)	
	excessive	(7.8%)	(4.1%)	(14.3%)	
Embryo class	no embryos	(14.3%)	(12.2%)	(17.9%)	0.020
	adequate (A + B)	(67.5%)	(63.3%)	(75.0%)	
	inadequate (C + D)	(18.2%)	(24.5%)	(7.1%)	
Pregnancy	no pregnancy	(59.7%)	(51.0%)	(75.0%)	0.040
	biochemical	(9.1%)	(10.2%)	(7.1%)	
	clinical	(31.2%)	(38.8%)	(17.9%)	
Pregnancy complications		(6.5%)	(0.0%)	(17.9%)	0.001
Pregnancy outcomes	Miscarriage	(1.3%)	(0.0%)	(3.6%)	0.005
	Ectopic pregnancy	(0.0%)	(0.0%)	(0.0%)	
	Live born child	(27.0%)	(39.0%)	(11.0%)	

Table 2: Reproductive outcomes in groups according to pre-treatment of endometriosis

Parameters	Total (%)	Group I (%)	GIA (%)	GIB (%)	Group II (%)	Between groups			
						GI/GII	GIA/GII	GIB/GII	GIA/GIB
Fertilization rate	55.70	59.50	60.80	58.02	48.59	0.357	0.372	0.506	0.723
Implantation rate	17.91	21.59	23.91	19.05	10.87	0.239	0.208	0.415	0.473
Pregnancy rate/started cycle	40.26	48.98	53.85	43.48	25.00	0.061	**0.040**	0.171	0.338
Live birth rate	27.00	39.00	41.00	33.00	09.00	**0.043**	**0.020**	0.055	0.511

Results

A total of 51 patients with endometriosis were included in the study and were divided into three groups. In the Group-IA, 17 patients had surgical treatment that was followed by medical treatment and in the Group-IB 17 patients were only surgically treated. The Group-II (control group) included 17 patients immediately subjected to the IVF. The average patients age was 34.14 ± 3.53 years (range 26–40 years). Average BMI was 22.55 ± 2.45 (range 18.5– 29.4). The mean ± SD patients age was similar in both groups (Group I 33.88 ± 3.20 years and Group II 34.43 ± 3.95 years; $p > 0.05$). Mean BMI was also comparable regarding patient groups (22.66 ± 2.44 GI and 22.66 ± 2.58 GII; $p > 0.05$). Average EFI score was 6.04 ± 1.96 in the GI with average cyst size 56.5 ± 13.54 mm, and EFI 5.86 ± 1.63 in control GII with average cyst size 25.3 ± 6.04 mm ($p < 0.001$).

Reproductive outcomes

Both FR and IR as well as PR per started cycle were higher in the Group-I with previously treated patients, but without statistical significance. Moreover, although FR, IR and PR were somewhat better in Group-IA patients, there were no statistically significant differences between subgroup A and B. B of GI concerning the examined outcomes. On the other hand, the LBR was significantly higher in the GI compared to G II (Tab. 2).

Pregnancies were statistically more frequent in the GIA compared to the GIB and to the GII control. Compared to the GIB there were more quality ovarian responses (47.8% vs 46.2%; $p = 0.436$) and quality (A and B) embryos (65.4% vs 60.9%; $p = 179$) in the GIA, but without statistical significance. The cycle cancelation was slightly more frequent in the control GII compared to the cycles in both GIA and GIB although this finding was also statistically not significant (Tab. 1 and 2)

The PR per started cycle was the highest in the GIA, and the lowest in the control GII (OR = 2.16; 95% CI.95 0.63– 7.35) ($p = 0.040$). There was no significant difference between the PR per started cycle in the GIB vs control GII (OR = 1.74; 95% CI.95 0.78–3.88). The LBR was significantly higher in the GIA compared to the GII ($p = 0.020$), but there was no difference between GIB compared to the control GII ($p = 0.055$). Compared success rates in both GIA and GIB and in the control GII are shown in the Table 2. Pregnancy complications and adverse outcomes (biochemical pregnancy, ectopic pregnancies and spontaneous abortion) were significantly more frequent in the GII (Tab. 1).

Statistical Analysis:

Descriptive statistics were used to summarize demographic, biochemical and clinical characteristics. The fertilization, implantation, clinical pregnancy and live birth rates were calculated as treatment success measures. Differences in investigated parameters between groups were tested by ANOVA or Kruskal-Wallis χ^2 test. Finally, we applied binary logistic regression (uni- and multivariable) to test the impact of endometriosis pre-treatment on pregnancy achievement and having a live born child. The values $p < 0.05$ are accepted as significant. Analyses were performed using SPSS for Windows version 22 (SPSS, Inc, Chicago, IL).

Discussion

Patients with advanced endometriosis (stages III/IV) have poorer reproductive outcomes of IVF in overall although the exact pathogenic mechanisms are still unclear [15]. Endometriosis is associated with a reduced number of retrieved oocytes and high-quality embryos, lower IR and PR possibly due to poorer endometrial receptivity, but LBR is approximately the same as for other causes of infertility [16–18]. Although the clinical PR after IVF may be reduced, the prognosis is better for minimal and mild endometriosis compared to severe stages even after surgical treatment [19]

Endometriosis treatment includes either medical or surgical options [4, 11, 12]. According to ESHRE even in stage I/II the complete surgical removal of endometriosis is recommended to improve LBR prior to IVF [11]. The pregnancy and live birth rates seem to be improved by surgical treatment of endometriosis regardless of its bilaterality, although it is associated with AFC [20]. Still, majority of authors suggest surgical treatment only for large symptomatic cases, as no clear benefit of minimal endometriosis removal in women undergoing IVF has been demonstrated . Another potential complication of surgery remains potential damage to ovarian reserve which may compromise IVF success

[6]. Nevertheless, other studies that neither surgical treatment nor endometriosis stage correlated with AFC [15].

In women with infertility and severe form of endometriosis thorough surgery may be followed by medical therapy as well. Patients in all stages of endometriosis require higher doses of gonadotropins for a longer duration compared to patients with tubal infertility [22]. This is particularly true for women with diminished ovarian reserve, while those with adequate reserve might be treated with standard doses of gonadotropins [15]. Some data show that PR and LBR per started cycle in fresh ET might be higher using protocols with the GnRH agonists, compared to the GnRH antagonist.

In our research the FR, IR, PR and the LBR were higher in the cycles of patients who were previously treated, compared to those who were directly subjected to the IVF even in the lower stages of endometriosis. In addition, our study proved that combined surgical and medical treatment was the optimal approach for endometriosis patients in order to obtain successful IVF reproductive outcomes. Moreover, we pointed out the potential factors that could affect the IVF outcome after combined surgical and medical therapy. Pregnancies from IVF procedures were mostly achieved in patients with less than 35 years of age, duration of infertility up to three years, lower EFI score and cycles using long protocol with FSH+HMG gonadotropins.

In the cycles of patients with higher ASRM score and endometriosis treatment, we more often used a combined administration of FSH and HMG. Interestingly, in the cycles of patients who did not have prior endometriosis treatment and with endometriomas up to 3 cm, we had slightly more cycles with good ovarian responses and better-quality embryos but without statistical significance. In these cycles a lower LBR was also observed. Further investigations to explain the lower LBR reason (impact of the operative technique itself or just the presence of endometriosis) are still needed.

Studies showed that a detrimental effect on the ovarian cortical tissue could be due to the mechanical stretching during surgery regardless of the endometrioma size [27, 28]. Surgery may decrease ovarian response, but some form of endometriosis treatment could help in the context of implantation such as use of the ultra-long protocols . Prolonged course of GnRH agonists prior to IVF may suppress the negative effect of the endometriosis on fertility and may also reduce the possibility of the disease recurrence [29]. The fact that administration of a prolonged course of GnRH agonists may improve IVF outcomes was also observed in this investigation. However, question remains how to treat patients with endometriomas smaller than 3 cm although IVF should be recommended [29].

The strength of this study was an individualization and continuity of the endometriosis treatment. For each patient, the surgery only or combined with medical therapy followed by the IVF were carried out depending on the basic findings of enrollment. Interventions were carried out in one center by one team, with no loss of patients during treatment and follow up. Moreover, the study novelty is the construction of models for IVF outcome prediction in endometriosis patients overall and depending on endometriosis treatment.

Several study limitations should be mentioned. The main limitation was the small final sample size for conclusions generalizability. The final sample was considerably smaller than the overall number of patients who were submitted to IVF in our Clinic during the study period. However, to overcome any potential confounding effects on IVF outcome, we set the strict inclusion criteria to investigate only the outcome of IVF in patients with primary infertility due to endometriosis and without any other associated infertility factors. Second, there were differences in the groups regarding age (younger and older) and endometriosis stage that could have affected results. Still, mean age did not significantly differ between patient groups. Third, as a criterion for surgical treatment (cyst size) we used ESHRE recommendations, but with the possibility of selection bias. Fourth, we analyzed different stimulation protocols in IVF cycles in a relatively small sample of patients. More reliable results could certainly be obtained by RCT, but with the complexity of this treatment in the single center setting it would be difficult to conduct

Conclusion

In conclusion, combined surgical and pharmacological endometriosis treatment had a significant positive impact on IVF reproductive outcomes (both PR and LBR) compared to patients without previous therapy or those treated only surgically. To enhance IVF success rates the use of long protocol with FSH+HMG gonadotropins in patients with shorter infertility duration and lower EFI score might be recommended. To achieve more reliable data on adjuvant therapy for endometriosis, further multicentric studies should be performed on a larger group of patients selected depending on endometriosis stage and using one specific stimulation protocol

Declarations:

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Conflicts of interest/Competing interests: None.

Availability of data and material: Department of Obstetrics & Gynaecology, LN Medical College & Research Centre, Bhopal.

Code availability: Not applicable.

Consent to participate: Consent taken.

Ethical Consideration: There are no ethical conflicts related to this study.

Consent for publication: Consent taken

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