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Reproductive outcomes of IVF after comprehensive endometriosis treatment: a prospective cohort study

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ABSTRACT

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

Material and methods: The study, conducted over a five year period, included 73 patients with endometriosis associated primary infertility subjected to 77 cycles. 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 25 patients, Group IB 21 and Group II 27 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 pretreatment 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.

Key words: endometriosis; infertility; IVF; minimally invasive surgery; reproductive outcome

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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 with oral contraception for 6–8 weeks before IVF [5]. Contrary, other studies found no fertility improvement with the use of different ovulation

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suppression agents or anti-inflammatory drugs for endometriosis treatment [6].

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.

Objectives

The study aim was to evaluate the impact of pharmacological and surgical endometriosis pretreatment on IVF reproductive outcomes in patients with primary endometriosis related infertility and normal ovarian reserve.

MATERIAL AND METHODS

Patients

This prospective cohort study was performed at the Clinic of Ob/Gyn, University Clinical Centre of Serbia over a five-year period, selecting patients with primary infertility caused by endometriosis to submit to IVF cycles. The study was approved by the Ethical Committee of the Faculty of Medicine University of Belgrade, Serbia, (Review Board Approval 61206-2616/2-2013). All patients signed an informed consent before study enrollment.

Inclusion criteria were: age ≤ 40 years, primary infertility caused by endometriosis, the absence of other associated infertility factors, body mass index (BMI) ≤ 30 kg/m^2, regular cycles (24–35 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 (Cetrotide®, Merck Serono) 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 FSH (follitropin α — Gonal F®, Merck Serono or follitropin β — Puregon®, MSD) and/or human menopausal gonadotropin (HMG) (menotropin — Menopur®, Ferring Pharmaceuticals) 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.

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).

RESULTS

Patients

During the study period, a total of 947 patients who had IVF procedure in Clinic were analyzed. Upon applying inclusion and exclusion criteria, a total of 73 patients with endometriosis were included in the study. These patients had 77 cycles of IVF whose outcomes were evaluated.

In the GIA, 25 patients had surgical treatment that was followed by medical treatment (34.2%) and in the GIB 21 patients were only surgically treated (28.8%). The GII (control group) included 27 patients (37%) immediately subjected to the IVF. Eleven cycles (14.3%) were cancelled. Description of the patients and IVF cycles in relation to the groups is shown in the Table 1.

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 ($p < 0.001$).

In the GI, authors recorded significantly higher number of patients with ≤ 35 years (67.3%), infertility duration under three years (65.3%) and ASRM III/IV stage of endometriosis (91.8%). In the control GII there were significantly more patients with endometriosis ASRM score < 16 (46.4%). In the GI FSH and HMG were more frequently used (55.1%).

Reproductive outcomes

Both FR and IR as well as PR per started cycle were higher in the GI with previously treated patients, but without statistical significance. Moreover, although FR, IR and PR were somewhat better in GIA patients, there were no statistically significant differences between subgroup A

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

Parameters		Total n = 73 patients IVF 77 cycles	Group I n = 46 patients IVF 49 cycles	Group II n = 27 patients IVF 28 cycles	Between groups p
Age ≤ 35		41 (56.2%)	31 (67.4%)	10 (37.0%)	0.004
Primary infertility > 3 years		35 (47.9%)	16 (34.8%)	19 (70.4%)	0.002
Body Mass Index ≤ 25		63 (86.3%)	40 (87.0%)	23 (85.2%)	0.680
EFI ≤ 7		50 (68.5%)	29 (63.0%)	21 (77.8%)	0.166
Endometriosis stage III–IV		56 (76.7%)	42 (91.3%)	14 (51.8%)	0.001
Presence of endometrioma		50 (68.5%)	44 (95.7%)	6 (22.2%)	0.001
Endometrioma > 3 cm		43 (58.9%)	39 (86.6%)	4 (14.8%)	0.001
ASRM score	< 16	17 (23.3%)	4 (8.7%)	13 (48.1%)	0.001
	16–40	35 (47.9%)	24 (52.2%)	11 (40.7%)	
	41–70	16 (21.9%)	14 (30.4%)	2 (7.4%)	
	≥ 71	5 (6.8%)	4 (8.7%)	1 (3.7%)	
Endometrioma localization	unilateral	36 (49.3%)	34 (73.9%)	2 (7.4%)	0.028
	bilateral	14 (19.2%)	10 (21.7%)	4 (14.8%)	
Protocol	Short + agonists	20 (26.0%)	14 (28.6%)	6 (21.4%)	0.442
	Short + antagonists	31 (40.3%)	20 (40.8%)	11 (39.3%	
	Long + agonists	26 (33.8%)	15 (30.6%)	11 (39.3%)	
Gonadotropins (IU)		2341.6 ± 776.4 (M = 2100.0)	2374.0 ± 831.4 (M = 2100.0)	2284.2 ± 680.2 (M = 2062.50)	0.388
Gonadotropins	FSH	31 (40.3%)	18 (36.7%)	13 (46.4%)	0.896
	HMG	12 (15.6%)	4 (8.2%)	8 (28.6%)	
	FSH + HMG	34 (44.2%)	27 (55.1%)	7 (25.0%)	
Number of aspirated oocytes		7.3 ± 5.5 (M = 5.5)	6.7 ± 4.9 (M = 5.00)	8.4 ± 6.2 (M = 7.00)	0.320
Cycle cancelation		11 (14.3%)	6 (12.2%)	5 (17.9%)	0.482
Ovarian response	poor	34 (44.2%)	24 (49.0%)	10 (35.7%)	0.676
	adequate	37 (48.1%)	23 (46.9%)	14 (50.0%)	
	excessive	6 (7.8%)	2 (4.1%)	4 (14.3%)	
Embryo class	no embryos	11 (14.3%)	6 (12.2%)	5 (17.9%)	0.020
	adequate (A + B)	52 (67.5%)	31 (63.3%)	21 (75.0%)	
	inadequate (C + D)	14 (18.2%)	12 (24.5%)	2 (7.1%)	
Pregnancy	no pregnancy	46 (59.7%)	25 (51.0%)	21 (75.0%)	0.040
	biochemical	7 (9.1%)	5 (10.2%)	2 (7.1%)	
	clinical	24 (31.2%)	19 (38.8%)	5 (17.9%)	
Pregnancy complications		5 (6.5%)	0 (0.0%)	5 (17.9%)	0.001
Pregnancy outcomes	Miscarriage	1 (1.3%)	0 (0.0%)	1 (3.6%)	0.005
	Ectopic pregnancy	1 (1.3%)	0 (0.0%)	1 (3.6%)	
	Live born child	22 (28.6%)	19 (38.8%)	3 (10.7%)	

IVF — in vitro fertilization; FSH — follicle stimulating hormone; HMG — human menopausal gonadotropin; ASRM — American Society of Reproductive Medicine; EFI — Endometriosis Fertility Index

and 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).

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

Parameters	Total (%)	Group I (%)	GIA (%)	GIB (%)	Group II (%)	Between groups p			
						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	27.27	38.78	42.31	34.78	10.71	**0.043**	**0.020**	0.055	0.511
Rate cycle cancellation	14.29	12.24	11.54	13.04	17.78	0.543	0.553	0.679	0.762

GI — group I with patients treated for endometriosis before the n vitro fertilization (IVF); GIA — group I subgroup A combined surgical and pharmacological treatment; GIB — group I subgroup B only surgical treatment; GII — control group II with patients immediately subjected to the IVF

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).

Regression analysis

In univariable logistic regression we confirmed that method of endometriosis pretreatment can impact pregnancy achievement in IVF (R^2 = 0.575; variance = 57.9%; p = 0.036). We also obtained significant models for pregnancy prediction adjusted for patient characteristics (R^2 = 0.623; variance = 96%; p = 0.002) and IVF characteristics (R^2 = 0.472; variance = 78.8%; p = 0.001). Pretreatment of endometriosis remains a significant predictor for pregnancy achievement, but infertility duration, EFI score, applied protocol and type of gonadotropins can influence this association.

In univariable logistic regression we confirmed that method of endometriosis pretreatment can affect live birth after IVF (R^2 = 0.582; variance = 91.7%; p = 0.008). However, we did not obtain significant models for live birth prediction neither when adjusted for patient characteristics (p = 0.338) nor IVF characteristics (p = 0.093).

The combined surgical and pharmacological endometriosis treatment had the optimal impact on IVF reproductive outcomes, both on PR and LBR. Shorter infertility duration, lower EFI score, the use of long protocol and FSH+HMG gonadotropins increase the possibility of successful IVF in pretreated endometriosis patients (Tab. 3 and 4).

Finally, we assessed parameters that could affect IVF outcomes in GI and GII separately. The only significant model was obtained for pregnancy prediction based on IVF characteristics in control GII patients (R^2 = 0.637; variance = 78.6%; p = 0.015). In patients not treated for endometriosis prior to IVF, ovarian response was the main prognostic parameter for pregnancy achievement (Tab. 5).

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 [16, 17, 21]. Another potential complication of surgery remains potential damage to ovarian reserve which may compromise IVF success [6]. Nevertheless, other studies found 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 [4, 11, 12]. 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

Table 3. Predictors of endometriosis patients achieving pregnancy after in vitro fertilization (IVF)

Parameters		B coefficient	Standard error	Wald coefficient	p	Odds ratio	95% Confidence Interval for B	
							Lower Bound	Upper Bound
Unadjusted model 1	(Constant)	1.017	0.719	2.000	0.015	2.765		
	Group I/II	–1.058	0.522	4.112	**0.043**	0.347	0.125	0.965
Unadjusted model 2	(Constant)	0.836	0.614	1.852	0.174	2.307		
	GIA/GIB/GII	–0.620	0.291	4.542	**0.033**	0.538	0.304	0.951
Model patient characteristics	(Constant)	–6.802	25.152	3.936	0.041			
	Group I/II	–2.734	5.101	4.051	**0.033**	3.391	0.006	4.008
	Age	–0.713	1.295	0.303	0.582	0.490	0.039	6.203
	BMI	0.795	0.573	1.923	0.165	2.214	0.720	6.811
	Infertility time	–5.144	2.543	4.092	**0.043**	7.472	1.174	8.053
	EFI score	–1.583	0.629	6.331	**0.012**	4.869	1.419	6.708
	Endomet stage	3.798	4.487	0.717	0.397	4.615	0.007	9.421
	Endomet place	–2.209	4.345	0.258	0.611	0.110	0.000	5.486
	Endomet size	5.893	13.397	0.946	0.392	6.665	0.748	1.336
Model IVF characteristics	(Constant)	4.721	2.566	3.384	0.046	1.238		
	Group I/II	–2.332	0.855	7.443	**0.006**	0.097	0.018	0.519
	Protocol type	0.939	0.468	4.023	**0.045**	2.557	1.022	6.402
	Gonadot type	0.483	0.211	5.257	**0.022**	0.617	0.408	0.932
	Aspirated Oo No	–5.789	13.397	0.839	0.453	0.003	0.786	1.617
	Ovary response	0.980	1.011	0.939	0.332	2.664	0.367	9.323
	Cycle canceled	0.930	0.771	1.624	0.551	2.324	0.756	4.352
	Embryo No	–0.012	0.143	0.007	0.933	0.988	0.747	1.307
	Embryo class	–0.906	0.726	1.556	0.212	0.404	0.097	1.678

Endomet — endometriosis; Oo — oocyte; Gonadot — gonadotropins; BMI — body mass index; IVF — in vitro fertilization; No — number; GI — group I with patients treated for endometriosis before the IVF; GIA — group I subgroup A combined surgical and pharmacological treatment; GIB — group I subgroup B only surgical treatment; GII — control group II with patients immediately subjected to the IVF

Table 4. Significant prediction models of endometriosis patients having a live born child after in vitro fertilization (IVF)

Parameters		B coefficient	Standard error	Wald coefficient	p	Odds ratio	95% Confidence Interval for B	
							Lower Bound	Upper Bound
Unadjusted model 1	(Constant)	–3.124	1.485	4.423	0.035	0.044		
	Group I/II	2.936	0.674	1.932	**0.045**	2.551	0.681	5.550
Unadjusted model 2	(Constant)	3.754	1.308	1.798	0.018	0.776		
	GIA/GIB/GII	–2.419	0.976	0.184	**0.048**	1.658	0.097	4.456

GI — group I with patients treated for endometriosis before the IVF; GIA — group I subgroup A combined surgical and pharmacological treatment; GIB — group I subgroup B only surgical treatment; GII — control group II with patients immediately subjected to the IVF

using protocols with the GnRH agonists, compared to the GnRH antagonist [23–26].

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

Table 5. Significant models of pregnancy after in vitro fertilization (IVF) prediction regarding endometriosis treatment

Parameters		B coefficient	Standard error	Wald coefficient	p	Odds ratio	95% Confidence Interval for B	
							Lower Bound	Upper Bound
Model IVF characteristics in Group II of not treated patients	(Constant)	–16.261	10.600	2.353	0.001	0.125		
	Protocol type	1.468	2.398	0.375	0.540	4.340	0.039	47.211
	Gonadot type	–0.696	1.593	0.191	0.662	0.498	0.022	11.324
	Aspirated Oo No	–0.355	0.276	1.655	0.198	0.701	0.408	1.205
	Ovary response	8.271	4.465	3.432	**0.046**	9.663	0.619	24.597
	Cycle canceled	–1.518	1.241	1.496	0.221	0.219	0.019	2.495
	Embryo No	–0.482	0.485	0.985	0.321	0.618	0.239	1.599
	Embryo class	2.138	2.225	0.924	0.337	8.486	0.108	66.916

Endomet — endometriosis; Oo — oocyte; Gonadot — gonadotropins; No — number; GII — control group II with patients immediately subjected to the IVF

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 [3, 11, 16]. 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, 30]. 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, 30].

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.

CONCLUSIONS

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.

Author contributions

Bila J, Tinelli A, and Vidakovic S designed and were responsible for carrying out the study; Bila J, Vidakovic S, Spremovic Radjenovic S and Stojnic J performed data collection and evaluation; Bila J, Dotlic J and Tulic L were responsible for the statistical analysis and literature review; Bila J, Micic J and Dotlic J wrote the final manuscript; Tinelli A, Spremovic Radjenovic S, Vidakovic S and Stojnic J critically revised the manuscript. All the authors reviewed, edited, and approved the final submission.

Ethics approval

The study was approved by the Ethical Committee of the Faculty of Medicine University of Belgrade, Serbia. All patients gave informed consent before enrollment, the signed informed consent for surgery and post-surgical follow up, and the group II patients chose a long-term clinical follow-up and pharmacological treatment.
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Conflict of interests

Authors certify that there is no actual or potential conflict of interest in relation to this article.

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