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GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Optimizing infertility treatment for ovarian endometrioma: is surgical intervention preferable before or after in-vitro fertilization programs?

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Abstract

Purpose Endometriosis is one of the common endometrial pathologies that occurs in reproductive-age women and could lead to infertility. This study set out to observe which clinical management of endometriosis with endometrioma is prominent in improving IVF outcomes.

Materials and methods This was a retrospective cross-sectional controlled study at Bunda General Hospital and Morula IVF Jakarta Clinic, Indonesia from Jan 2018 to Dec 2022. A total of 279 patients diagnosed with endometriosis were recorded. Of that, 86 couples with endometrioma underwent an in vitro fertilization program (IVF). Forty-eight women performed IVF prior to the removal of endometrioma through surgery (IVF-OPS) while the remaining underwent surgery for endometrioma removal followed by an IVF program (OPS-IVF). Each group was compared to the control group which was administered to an IVF program without the removal of endometriosis. The primary outcome was the clinical pregnancy rate. Mann–Whitney or Kruskal–Wallis and Chi square were used for statistical analysis. A p value of <0.05 was considered statistically significant.

Results A comparable clinical pregnancy rate was observed across the three groups ($p=0.068$). Nonetheless, the IVF-OPS approach led to an improved number of top-quality blastocysts compared to both the control and OPS-IVF groups ($p<0.05$). Eventually, IVF-OPS was shown to be a prominent approach for endometriosis with endometrioma management in comparison to OPS-IVF in terms of clinical pregnancy rate as well as embryology laboratory outcomes ($p<0.05$).

Conclusion Our result suggested that intervention of endometriosis with removal surgery was superior when performed after the IVF program.

Keywords Endometriosis · Infertility · In-vitro fertilization program · Surgery

What does this study add to the clinical work

Performing surgery after IVF program (IVF-OPS) yields better outcomes, emphasizing the importance of timing in surgical intervention for endometrioma patients undergoing IVF. Surgery before IVF (OPS-IVF) results in poorer embryology lab outcomes, suggesting it may be less effective for improving fertility outcomes.

Introduction

Approximately 30% to 50% of women with endometriosis experience infertility [1]. The potential mechanisms behind this correlation involve pelvic anatomical distortion impacting ovarian physiological function and an

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unfavorable peritoneal environment due to inflammation, which may alter oocyte quality [2]. Notably, endometriosis manifests in three phenotypes including ovarian endometriosis namely endometrioma (OMA), superficial peritoneal lesions (SUP), and deep endometriosis. OMA represents up to 44% of all sub-type cases of endometriosis [3] and may occur in one or both ovaries [4]. A common diagnosis tool for OMA involves ultrasound examination which typically reveals the presence of unilocular or multilocular cysts containing fluid with low-level echogenicity, a characteristic appearance under ultrasound imaging. Infertility management of endometrioma usually requires surgical intervention by considering the patient's age, surgical approach, and localization of the disease. The 2013 ESHRE guidelines recommend laparoscopic excision with a stripping technique for endometriomas larger than 3 cm. However, they note that there is no strong evidence supporting the benefit of surgery prior to assisted reproductive technology. Furthermore, the excision of the cyst wall during surgery often results in the reduction of ovarian tissue [3].

The clinical impact of endometrioma surgery intervention has been demonstrated in several studies indicating Anti-Mullerian hormone (AMH) is of established marker rather than Antral follicle count (AFC) to evaluate postoperative endometrioma on ovarian reserve. It has been reported consistently that decreased AMH levels occurred post-surgery [5–7]. To date, no guidelines are providing the best management for managing infertility-related endometrioma [8]. This study aimed to retrospectively compare the clinical outcomes of two different management of ovarian endometrioma by comparing endometrioma through surgery (IVF-OPS) and endometrioma removal followed by an IVF program (OPS-IVF) with the control group.

Materials and methods

Research participant

This retrospective cross-sectional study took place at Morula IVF Jakarta Clinic and Bunda General Hospital, Indonesia from Jan 2018 to Dec 2022. A total of 279 patients diagnosed with endometriosis underwent removal surgery at Bunda General Hospital, affiliated with Morula IVF Clinics. The diagnosis of endometriosis was confirmed through pathological anatomy reports. Among these patients, 86 couples underwent an IVF program. Of these, 48 women underwent IVF followed by endometrioma removal surgery (IVF-OPS), while 38 women underwent endometrioma removal surgery prior to IVF (OPS-IVF). Each group was compared to a control group diagnosed with endometriosis and the presence of endometrioma, who underwent the IVF program at Morula IVF Jakarta Clinic without a history of surgical removal. Endometriosis diagnosis in IVF-OPS and OPS-IVF was confirmed through pathology histological report while in the control group, endometriosis was confirmed through ultrasound judged by a certified fertility specialist in our IVF clinic. All variables were retrieved from Morula IVF Jakarta Clinic databases. The primary outcome measured was the clinical pregnancy rate. Statistical analysis was performed using Mann–Whitney or Kruskal–Wallis and Chi-square with a significance level set at $p < 0.05$. The research protocol was submitted and reviewed by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia. Research approval was obtained with the approval number KET-593/UN2.F1/ETIK/PPM.00.02/2022 and the need for informed concern was waived.

Ovarian stimulation, ovum pick-up, and embryo culture

Studied participants underwent antagonist, agonist long protocol, and mild stimulation as described in our previous research [9]. Briefly, in the antagonist protocol, ovarian stimulation was commenced on day 2 or 3 of menstrual cycles after evaluation of reproductive basal hormone including FSH, LH, and Estradiol levels. The type of gonadotropins utilized were either Gonal-F (Merck Serono), Pergoveris (Merck Serono), Menopur (Ferring), or a combination of those drugs with starting doses ranging from 150 to 375 IU. Antagonist injection of 0.25 mg Cetrotide (Merck Serono) started on day 5 of stimulation. In an agonist-long protocol, 250 pg GnRH-agonist was administered on the 21 days of menstrual cycles for a minimum of 10 days consecutively. Gonadotropin stimulation started when follicles of size < 5 mm and E2 level of < 80 pg/mL and progesterone level of < 1 ng/mL were detected and the injection of GnRH agonist was continued until the injection of follicle triggered maturation. In mild stimulation, administration of clomiphene citrate started on day 2 or 3 of menstrual cycles followed by daily injection of gonadotropin and GnRH antagonist until the day of ovulation trigger injection. In all protocols, injection of 250 mcg rhCG (Ovidrel, Merck) was conducted when at least 3 follicles had reached 17–18 mm in diameter. The ovum pick-up procedure was conducted under sedation 36–38 h after maturation injection. Oocytes were aspirated through ultrasound visualization with a mounted negative pressure needle on the transvaginal transducer. All retrieved mature oocytes were fertilized through either intra-cytoplasmic injection (ICSI) or intra-morphologically selected sperm injection (IMSI). A time-lapse incubator was used for embryo culture (Miri TL, 37^0C, 6% CO_2, 5% O_2).

Embryo transfer was conducted on either cleavage or blastocysts stage depending on the number of available good embryos on day three of embryo culture assessment as previously described [10].

Endometriosis surgery procedures

Surgeries were conducted at Bunda General Hospital Jakarta Indonesia. The surgeon (IVN, AJ, AAP, IRH, BS) performing the procedure is a fertility specialist certified in advanced laparoscopy and robotic minimally invasive surgeries with over 10 years of experience. All laparoscopy and robotic surgeries were conducted under general anesthesia. Robotic surgeries were performed using DaVinci Si (Intuitive,USA) surgical platform. Adhesiolysis and peritoneal endometriosis were excised completely using either electrocautery or Harmonic ultrasonic instrument (Johnson & Johnson, USA). Endometriosis cysts were removed with the stripping technique previously described [11]. All samples were sent for histopathology for confirmation.

Outcomes measure and statistical analysis

Clinical pregnancy was the primary outcome defined as the detection of at least a single fetal heartbeat through ultrasound measurement [9]. Calculation of clinical pregnancy on OPS-IVF and control group was calculated in fresh embryo transfer cycles. On the other hand, clinical pregnancy calculation in IVF-OPS patients was retrieved from frozen cycles as most embryos were frozen immediately after D3 or D5 embryo culture. Statistical analysis was performed utilizing SPSS software version 26.0. Kolmogorov Smirnov was used for data normality distribution test. Data were presented as mean ± SD or median (Q1, Q3) depending on data distribution. Proportional/categorical data between groups was compared using Chi-Square, while the numerical data comparison utilized the Mann–Whitney or Kruskal–Wallis test. All data presented with a 95% CI.

Results

Table 1 presents the baseline characteristics of the studied participant. Median female age, infertility duration, and proportion of the types of female infertility were comparable among the three groups ($p > 0.05$). Body mass index (BMI) was statistically significant among the three groups in which women in the OPS-IVF group had a low BMI in comparison to the control group ($p = 0.038$). Comparable clinical characteristics were observed in several parameters including basal hormone levels of FSH, LH, estradiol, and progesterone as well as estradiol and progesterone levels on the trigger day. Antral follicle count, proportion of ovarian stimulation protocol, starting gonadotropin dosage, total gonadotropin usage, and endometrial thickness were also comparable among groups. On the other hand, a noteworthy difference was observed among the study groups in terms of ovarian stimulation duration ($p < 0.05$). In addition, the AMH levels differed significantly among the three groups, with OPS-IVF showing lower levels compared to IVF-OPS and the control group when measured after removal surgery ($p < 0.05$). The size of endometrioma between the IVF-OPS and OPS-IVF groups demonstrated no significant difference. However, the median cyst(s) size in the control group was significantly smaller than that of both surgery groups. This finding elucidates the reason why infertility specialists may not prioritize surgery for the presence of endometrioma in women in the control group.

The clinical pregnancy rate among the three groups did not differ (24/48 (50%), 10/38 (26.3%), and 17/49 (34.7%), respectively, for IVF-OPS, OPS-IVF, and control group, $p = 0.068$). However, sub-group analysis between IVF-OPS in comparison to OPS-IVF demonstrated a noteworthy clinical pregnancy rate (24/48 (50%) vs. 10/38 (26.3%) respectively, $p = 0.029$). A logistic regression model was constructed to determine the impact of surgery timing intervention. After adjusting for AMH variables, a notable difference remains observed between the IVF-OPS and OPS-IVF groups ($p = 0.041$, OR 2.73, 95% CI 1.04–7.17)**.**

The laboratory outcome comparison between overall groups and between IVF-OPS and OPS-IVF were presented in Table 2. There were no differences among all groups in terms of the number of retrieved oocytes and the number of total embryos being transferred ($p > 0.05$). However, notable differences were observed in the number of injected and fertilized oocytes, the number of embryos at both cleavage and blastocysts stages as well as both top-quality cleavage and blastocysts stages. The overall analysis demonstrated comparable IVF laboratory outcomes between the IVF-OPS and control group ($p > 0.05$) but favorable IVF laboratory outcomes in comparison to that of the OPS-IVF group ($p < 0.05$).

Discussion

The present study highlighted the favorable outcomes of opting for IVF prior to undergoing endometriosis removal surgery as a leading approach to managing infertility. Implementation of a strategy termed IVF-OPS, wherein all embryos obtained from IVF cycles were cryopreserved, followed by patients undergoing endometriosis removal surgery via either robotic or conventional laparoscopy. Subsequently, after approximately three months, patients underwent embryo transfer during frozen cycles. Although clinical pregnancy rates were not significantly different

Table 1 Summary of baseline and clinical characteristics of the present study

Baseline and clinical characteristics	Group study			*p* value	
	IVF—OPS ($n=48$)	OPS—IVF ($n=38$)	Control ($n=49$)	IVF-OPS vs. OPS-IVF	All groups
Baseline characteristics					
Female age (years)	33 (31, 37)	34 (32, 39)	35 (32, 39)	0.178	0.179
Infertility duration (years)	4 (3, 8)	5.5 (4, 9)	6 (3, 5)	0.163	0.205
Body mass index (kg/m^2)	23.39 (20.85, 26.46)	22.23 (20.68, 24.40)[b]	24.62 (22.30, 27.29)	0.241	*0.038*
Type of female infertility					
Primary	42 (87.5%)	32 (84.2%)	41 (83.7%)	0.758	0.852
Secondary	6 (12.5%)	6 (15.8%)	8 (16.3%)		
Clinical characteristics					
Ovarian stimulation protocol					
Antagonist	42 (87.5%)	36 (94.7%)	49 (100%)		0.071
Long protocol	3 (6.25%)	0 (0.0%)	0 (0%)	0.068	
Mini stimulation	3 (6.25%)	2 (5.3%)	0 (0%)		
Basal FSH (mIU/mL)	7.39 (5.98, 8.55)	7.36 (6.25, 9.32)	7.43 (6.37, 8.83)	0.596	0.717
Basal LH (mIU/mL)	5 (3.6, 6.5)	5.45 (3.5, 6.9)	5 (3.9, 6)	0.944	0.939
Basal Estradiol (pg/mL)	34.3 (30.52, 41.62)	34.33 (26.55, 52.87)	32.46 (21, 48.61)	0.845	0.626
Basal Progesterone (pg/mL)	0.17 (0.07, 0.28)	0.14 (0.06, 0.24)	0.13 (0.07, 0.21)	0.720	0.650
AMH (ng/mL)	2.10 (1.27, 3.63)[a*]	1.06 (0.64, 1.68)[b*]	2.10 (1.13, 3.16)	*0.002*	*0.001*
Estradiol on trigger day (pg/mL)	2269 (1432, 3719	1685 (1319, 2420)	2140 (1539, 2835)	0.095	0.112
Progesterone on trigger day (pg/mL)	0.71 (0.40, 1.08)	0.57 (0.32, 0.77)	0.64 (0.45, 0.87)	0.145	0.252
AFC	10 (6, 13)	7 (5, 10)	9 (7, 12)	0.073	0.155
Endometrial thickness (mm)	10.1 (9.2, 12.8)	10.3 (8.9, 11.3)	11 (9.6, 12)	0.517	0.618
Starting dose	300 (300, 300)	300 (225, 300)	300 (225, 300)	0.340	0.558
Stimulation duration (day)	9 (8, 9)[a]	9 (9, 10)	9 (8, 9)	0.095	*0.043*
Total gonadotropin used (IU)	2400 (2100, 2700)	2700 (2325, 3000)	2400 (2025, 2700)	0.424	0.395
Size of endometrioma (cm)	4 (4, 7)[b]	4 (4, 6)[b]	2 (1, 4)	0.555	< 0.001

Data are presented as median (Q1, Q3), *n* (%). Kruskal–Wallis test is used for numerical variables between the three groups and Mann–Whitney between IVF-OPS and OPS-IVF. Chi-square tests are used for the categorical variable. [a]Compared with the OPS-IVF group, [b]compared with control. **p* value between the two groups was 0.002. AMH level in the OPS-IVF group presented in Table 1 was measured post-endometrioma removal surgery

Table 2 Comparison of laboratory outcomes between IVF-OPS and OPS-IVF group

Laboratory outcome	Group study			*p* value	
	IVF-OPS ($n=48$)	OPS—IVF ($n=38$)	Control ($n=49$)	IVF-OPS and OPS-IVF	All groups
Number of retrieved oocytes	11 (6, 14)[a]	6 (4, 10)	8 (5, 13)	*0.031*	0.070
Number of injected oocytes	8 (5, 11)[a]	4 (3, 8)	6 (4, 10)	*0.014*	*0.032*
Number of fertilized oocytes	6 (4, 8)[a]	3 (2, 6)	4 (3, 7)	*0.006*	*0.014*
Number of cleavages	6 (4, 8)[a]	3 (2, 6)	4 (3, 7)	*0.006*	*0.014*
Number of top cleavage quality	3 (1, 4)[a]	2 (1, 2)	2 (1, 4)	*0.008*	*0.026*
Number of Blastocyst	6 (3, 8)[a]	2 (1, 6)	4 (1, 7)	*0.002*	*0.006*
Number of top blastocyst quality	2 (1, 3)[a,b]	1 (0, 2)	1 (0, 2)	*< 0.001*	*< 0.001*
Number of total transferred embryos	1 (1, 2)[a]	2 (1, 2)	2 (1, 2)	*0.001*	0.358

Data were presented as median (Q1, Q3), *n* (%). Kruskal–Wallis or Mann–Whitney tests are used for numerical variables. [a]compared with OPS-IVF, [b]compared with control

between the three groups, initiating IVF before surgery, rather than surgery before IVF, seemed to result in better clinical pregnancy outcomes (50% vs. 26.3% respectively, $p = 0.029$). Moreover, our study found lower AMH levels in the OPS-IVF group measured after surgery, consistent with previous research [5–7]. In terms of stimulation duration, our study supports the previous finding [12], which indicated that the OPS-IVF group had a longer stimulation duration compared to the IVF-OPS group.

Endometriosis is generally known to reduce the ovarian reserve [13, 14]. Endometriotic cysts contain high levels of proteolytic enzymes, pro-inflammatory cytokines, reactive oxygen species (ROS), and free iron that may intervene in the expression of pivotal genes responsible for normal folliculogenesis. When these toxic contents are released to the ovaries, ROS abundance is elevated in the ovarian cortex, and necrosis of early follicles occurs. High levels of ROS further suppress ovarian angiogenesis and induce ovarian interstitial microvascular injury, leading to a condensing in blood perfusion to the ovarian cortex that ultimately ends in reduced ovarian reserve. [15] Thus, the removal of endometrioma through surgical intervention theoretically creates a more favorable environment for successful pregnancy [16]. However, a reduction in ovarian reserve was observed in patients who had undergone endometrioma resection. These patients already exhibited reduced ovarian reserve due to endometriosis per se, as reflected by reduced AMH level [5–7, 17].

AMH is secreted exclusively by granulosa cells which function to inhibit FSH-dependent follicle growth and initial follicular recruitment from the resting pool [18]. A study investigating the correlation between AMH level and oocyte quality demonstrated that serum AMH level was correlated positively with the number of mature oocytes [19]. A recent retrospective study comparably exemplified a meaningful correlation between AMH level and the number of aspirated follicles, the number of retrieved oocytes, and the number of mature oocytes [20]. An in vitro maturation on mouse oocytes found that supplementation of recombinant human AMH on culture medium significantly enhanced the mRNA and protein expression of growth differentiation factor-9 (GDF9) and bone morphogenetic protein-15 (BMP15) in a dose-dependent manner [21]. GDF-9 and BMP-15 are members of the TGFβ superfamily, which play a critical role in oocyte maturation. In addition to the lower number of retrieved oocytes, we presumed that the lower number of injected and fertilized oocytes in the OPS-IVF group compared to the IVF-OPS group in the present study may be due to reduced AMH levels following endometrioma removal in the OPS-IVF group. Reduces AMH levels likely led to the downregulation of GDF-9 and BMP-15 and impaired oocyte maturation process.

In terms of IVF outcomes, the benefit of surgical intervention for endometriosis is still a matter of debate. Several reports suggest that endometrioma removal does not improve IVF results and pre-cycle surgical resection of endometrioma does not enhance IVF outcome [22–24]. In contrast, a meta-analysis revealed that higher pregnancy rates per patient, pregnancy rates per cycle, and live birth rates per patient were significantly higher in patients who underwent surgery prior to IVF compared to the counterpart participants [25].In the present study, we found that the number of cleavages and blastocysts, as well as the number of top-quality cleavages and blastocysts, was significantly higher in the IVF-OPS group compared to the OPS-IVF group and the control group.

Removal of endometrioma theoretically could promote follicular development by lessening the tension in the ovarian tissue and reducing inflammatory factor levels in follicular fluid thus restoring normal ovarian anatomy and function. However, it has been demonstrated that healthy ovarian tissue containing primordial and preantral follicles is removed during endometrioma excision [26]. Moreover, hemostatic efforts during surgery may also damage the vascularity of the remaining healthy ovarian tissue resulting in reduced ovarian reserve as embodied with a significant decrease in postoperative AMH level [7, 27]. Although the effect of AMH on embryos remains elusive, some reports found that serum AMH levels were positively correlated with good-quality embryos [28]. As such, it seemed that a higher embryo quality of the IVF-OPS group in the present study could be assignable to the unaltered AMH level.

Overall, our findings demonstrate that the removal of endometrioma reduces the ovarian reserve emphasizing previous results. Despite surgery remaining the standard therapy for endometriosis, this must be carefully considered during IVF, especially in women who have already diminished ovarian reserve. This study has some potential limitations that need consideration. One of which was that women with irregular menstruation and women showing the presence of hydrosalpinx in ultrasound were not excluded from the study which may interfere with the result due to coexisting multimorbid condition. Additionally, AMH levels in participants of the OPS-IVF group were measured after surgery, without prior knowledge of their levels before the surgery. In conclusion, our study suggests that opting for IVF prior to endometriosis removal surgery results in a more favorable IVF outcome compared to endometriosis removal followed by an IVF program.

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commented on the previous version of the manuscript. All authors read and approved the final manuscript.

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Data availability The dataset pertaining to this study is available upon reasonable request to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no competing interest to disclose.

Ethics approval The study protocol was approved by the Ethics Committee of the Faculty of Medicine University of Indonesia (KET-593/UN2.F1/ETIK/PPM.00.02/2022).

Consent to participate Not applicable.

Consent to publish Not applicable.

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