ORIGINAL ARTICLE

Prognostic factors for IVF-ICSI live birth rate in women with endometriosis-related infertility

Min Ping Tew, Ahmad Shukri Rahilah, Shafie Rosliza

Reproduction Unit, Department of Obstetrics and Gynaecology, Sultanah Bahiyah Hospital, Alor Setar, Malaysia

ABSTRACT

Introduction: The present study aims to identify the factors contributing to diminished successful cumulative live birth rate (LBR) of in-vitro fertilisation-intra-cytoplasmic sperm injection (IVF-ICSI) among patients with endometriosis.

Materials and Methods: In this study, a retrospective cohort investigation was conducted from January 2016 to December 2022 at the Reproductive Medicine Center, Department of Obstetrics and Gynaecology, Sultanah Bahiyah Hospital, Alor Setar, Malaysia. Various determinants influencing substandard cumulative IVF-ICSI LBR prognosis in women diagnosed with endometriosis were analysed. A total of 157 patients, representing 214 IVF-ICSI cycles and 231 embryo transfers, were involved in the current study. The cumulative LBR per cycle was the primary outcome established.

Results: The present study recorded 25.7% (n=55) cumulative LBR per cycle. Prolonged infertility (95% confidence intervals, 95%CI: 0.33, 0.86, p=0.009), moderate to severe endometriosis (95%CI: 0.001, 0.39, p=0.009), and adenomyosis (95%CI: 0.013, 0.98, p=0.048) were factors that significantly reduced the cumulative LBR.

Conclusion: A prolonged infertility duration, the presence of adenomyosis, and moderate to severe endometriosis negatively impacted the cumulative LBR in IVF-ICSI treatments for women with endometriosis. Consequently, early aggressive infertility treatments for patients diagnosed with endometriosis are recommended.

KEYWORDS:
Endometriosis, infertility, IVF, live birth, prognosis.

INTRODUCTION

Endometriosis is characterised by endometrium-like tissue outside the uterus and a chronic inflammatory illness.[1] Primarily, the disease affects females of reproductive age, with an estimated 10 to 15% prevalence.[2,3] Approximately 25 to 50% of infertile women are diagnosed with endometriosis, while 30 to 50% of endometriosis patients experience infertility.[4]

Although historically, endometriosis was believed to affect Caucasians predominantly,[5] recent studies yielded conflicting results regarding racial and ethnic differences in its prevalence.[6-8] Similarly, a report on infertile patients undergoing diagnostic laparoscopy conducted simultaneously in Southeast Asia (Malaysia) and the United Kingdom revealed a considerably higher prevalence of endometriosis among Malaysian women.[8]

Despite being established as affecting fertility, the precise pathophysiology of endometriosis remains unknown. Contemporary perspectives suggest multifactorial mechanisms to explain the effects of the disease, including peritoneal fluid inflammatory alterations which change sperm-oocyte interactions, diminish functional ovarian tissue, and compromise endometrial receptivity.[9]

Typically, assisted reproductive technologies (ART) are employed to manage endometriosis-related infertility. Nevertheless, endometriosis is significantly linked with unsatisfactory in-vitro fertilisation-intra-cytoplasmic sperm injection (IVF-ICSI) results despite its widespread employment in endometriosis patients. Studies also indicated that endometriosis patients exhibited reduced clinical pregnancy rates, ovarian responses, and egg retrieval rates and increased gonadotropin demand than tubal infertility patients.[10-12]

Limited reports are available on identifying prognostic factors in endometriosis patients undergoing IVF-ICSI.[13-15] Furthermore, no studies have assessed the prognostic factors of Southeast Asian endometriosis patients. Consequently, this study aimed to evaluate the prognostic factors influencing the cumulative life birth rate (LBR) in IVF-ICSI among women with endometriosis in the Reproductive Medicine Center, Department of Obstetrics and Gynaecology, Sultanah Bahiyah Hospital, Alor Setar, Malaysia. The present study could be instrumental in counselling local endometriosis patients who seek ART treatment.

MATERIALS AND METHODS

This study obtained ethical approval from the National Medical Research Register (NMRR ID-23-02786-OMI).

The current retrospective study involved 157 subfertile patients from the Reproductive Unit of Department of Obstetrics and Gynaecology, Hospital Sultanah Bahiyah, Alor Star, Kedah, Malaysia. The data were collected from January 2016 to December 2022. The women selected to participate in this study had endometriosis, received IVF-ICSI

treatment, and were between 18 and 40 years old. Nevertheless, patients with body mass index (BMI) ≥33kg/m² or uterine anomalies were excluded.

The personal history and fertility data of each patient were obtained prior to receiving the ART treatment. The information procured included age, race, BMI, infertility type and duration, antral follicle count (AFC) via ultrasonography, presence or absence of other infertility causes (such as tubal or male factors), and the presence of adenomyosis during IVF. This study defined AFC as the total number of antral follicles observed in both ovaries utilising transvaginal ultrasonography during the early follicular phase. Only antral follicles between 2mm and 10mm in mean diameter in the most significant two-dimensional plane across the surface of the ovary were considered for this study.[16]

The current study documented the history and number of endometriosis surgeries before the women received ART treatments, the stage of endometriosis, recurrent endometrioma during IVF, and the interval between surgery and ART. The endometriosis staging was based on the Revised American Fertility Society Classification of Endometriosis guidelines, which were documented during the laparoscopic/laparotomy cystectomy procedure. Whereas, for the ART protocols, this study assessed the IVF attempt rank, controlled ovarian stimulation (COS) protocol, ovarian stimulation period, gonadotropin total dose, retrieved oocyte number, fertilisation rate (number of fertilisations divided by number of mature oocyte), endometrial thickness and numbers of fresh and frozen-thawed embryos transferred.

The COS Protocols
The current study employed the ultralong (gonadotropin releasing hormone [GnRH] agonist administered 3 to 6 months before stimulation), long (GnRH agonist administered during the luteal phase of the previous menstrual cycle) or antagonist (daily administration of GnRH antagonist from day fifth of stimulation) COS procedures. The gonadotropins utilised included recombinant follicle stimulating hormone (r-FSH), follitropin alpha (Gonal F®) and follitropin beta (Puregon®), human menopausal gonadotropin (Menopur®) and r-FSH and recombinant luteinising hormone (r-LH), which combined follitropin alpha and lutropin alpha (Pergoveris®).

The age, total AFC, BMI and previous stimulation dose (if applicable) of the participants in the present study influenced the initial gonadotropin doses administered. In contrast, follow-up doses during the IVF cycle were determined with transvaginal ultrasound. The gonadotropin dosage was adjusted based on the ovarian response during follicular tracking, where the expected follicular growth rate was between 1mm/day and 3mm/day. The GnRH agonist or antagonist and gonadotropin administration were continued until the day of human chorionic gonadotropin (HCG) issuance.

In this study, the patients were given either 10,000 international unit (IU) urinary HCG intramuscularly or recombinant-derived HCG (r-HCG) subcutaneously. The hormone was injected when at least three follicles reached a 17 mm mean diameter. Guided by transvaginal ultrasound, oocyte retrieval was performed 36 hours after HCG administration under local or general anaesthesia. A fresh semen sample from the husband was also obtained on the same day.

Intracytoplasmic sperm injection (ICSI) was performed after denudation and incubating the oocyte-corona complexes for four hours. On the other hand, the luteal phase was supported by daily vaginal progesterone. Progesterone was supplied starting on the oocyte retrieval day until a pregnancy blood assessment was conducted. In this study, fresh embryo transfers typically occurred between 48- and 72-hours post-oocyte retrieval under ultrasound guidance.

In this study, the frozen-thawed embryo transfer (FET) methodology utilised included the modified natural, mild stimulated and artificial cycle approaches. The present study monitored follicular growth in a modified natural cycle via transvaginal ultrasound from the 10th cycle day onwards. Similarly, in the mild stimulated approach, monitoring was initiated from cycle day 10 post daily oral administration of 5mg letrozole during cycle days 2 to 6 to induce mono-follicular growth. The patients subjected to the procedure were regularly monitored every 2 days.

When the dominant follicle recorded a diameter ≥17 mm, HCG was administered to trigger ovulation in the participants. Subsequently, exogenous progesterone was supplied vaginally, starting two days following HCG administration. The embryo transfer period was determined based on the embryo freezing day (5 and 7 days post-HCG administration for 3-day-old embryos and blastocysts, respectively).

In the current study, each participant in the artificial cycle was given 6 mg of oral oestradiol daily with or without prior pituitary suppression with long-acting agonists. Ten days later, an ultrasound evaluation was conducted to measure endometrial thickness and ensure no dominant follicle emerged. Vaginal progesterone suppositories were initiated once the endometrial thickness reached ≥7mm. Embryo transfers were performed three days post-progesterone administration for day-3 embryos, while for blastocysts, 5 days after.

Initially, this study considered pregnancy when a positive plasma HCG level on day 13 after cleavage stage (day-3 embryo) transfer or day 11 after blastocyst transfer. Subsequently, clinical pregnancy was confirmed via ultrasonographic visualisation of one or more gestational sacs, ectopic pregnancy, singleton or twins. Conversely, a miscarriage was defined as pregnancy loss before completing 22 gestational weeks. The present study also recorded delivery of a fertilisation product post completing 22 weeks of gestational age as live birth.

Assessment of Outcomes
Primary objective of our study was determining the cumulative LBR per IVF-ICSI cycle and transfer. This study calculated the cumulative LBR after fresh and frozen embryo transfers for each cycle across the entire population. Furthermore, the characteristics of women who conceived

Table I: The study population and IVF cycle characteristics (total population = 157 and number of cycles = 214).

	n (%)	Mean (Standard Deviation)
Age on the day of ART (years)		32.56 (3.80)
Age group (years)		
< 35	151 (70.6)	
≥ 35	63 (29.4)	
Race		
Malay	192 (89.7)	
Chinese	10 (4.7)	
Indian	7 (3.3)	
Others	5 (2.3)	
BMI		24.36 (4.22)
Infertility duration (years)		6.00 (4.00)*
Infertility types		
Primary	184 (86.0)	
Secondary	30 (14.0)	
Associated tubal factor		
No	136 (63.6)	
Yes	78 (36.4)	
Associated male factor		
No	172 (80.4)	
Yes	42 (19.6)	
History of surgery		
No	12 (5.6)	
Yes	202 (94.4)	
Number of surgeries		
None	12 (5.6)	
One	131 (61.2)	
Two or more	71 (33.2)	
Interval between surgery and ART		
No surgery	12 (5.6)	
< 2 years	130 (60.8)	
≥ 2 years	72 (33.6)	
Associated adenomyosis		
No	129 (60.3)	
Yes	85 (39.7)	
Endometriosis stage**		
I and II	35 (16.4)	
III and IV	149 (69.6)	
Clinical	12 (5.6)	
Unknown (no data)	18 (8.4)	
The rank of IVF attempt		
1st cycle	157 (73.4)	
2nd cycle	50 (23.4)	
3rd cycle	7 (3.2)	
Presence of endometrioma during cycle		
No	139 (65.0)	
Yes	75 (35.0)	
Size of endometrioma during cycle		
< 3 cm	55 (73.3)	
≥ 3cm	20 (26.7)	
COS protocol		
Ultralong agonist	150 (70.1)	
Short antagonist	48 (22.4)	
Long agonist	16 (7.5)	
Antral follicle count (AFC)		8.00 (5.00)*
AFC		
< 5	26 (12.1)	
≥ 5	188 (87.9)	
Gonadotrophin usage		
Only r-FSH	55 (25.7)	
Only hMG	13 (6.1)	
r-FSH + hMG	104 (48.6)	
r-FSH + r-LH	42 (19.6)	
Total gonadotrophin dose		2775.00 (1221.88)*
Duration of controlled ovarian stimulation		10.75 (1.58)
Number of retrieved oocyte		5.00 (4.00)*
Number of mature oocyte		4.00 (3.00)*
Number of fertilisation		3.00 (3.00)*
Fertilisation rate mean		0.86 (0.19)*

Table I: The study population and IVF cycle characteristics (total population = 157 and number of cycles = 214).

	n (%)	Mean (Standard Deviation)
Number of cycle cancelation	1	
Failure to retrieve oocyte	7	
Number of no embryo transfer	10	
Cycles of embryo transfer (ET)		
Number of fresh embryos transferred	153 (66.2)	
Number of frozen-thawed (FET) embryos transferred	78 (33.8)	
FET protocol (n=78)		
Artificial	48 (61.5)	
Stimulated	14 (17.9)	
Natural	16 (20.5)	
Number of embryo transfer		2.02 (0.65)
Day of embryo transfer		3.23 (1.02)
Endometrial thickness (mm)		11.27 (2.36)
Clinical pregnancy per ET cycle		
Fresh	52/153 (34.0)	
FET	21/78 (26.9)	
Miscarriage rate per ET cycle	16/73 (21.9)	
Multiple gestation rate per ET cycle	18/73 (24.7)	
Live birth per ET cycle		
Fresh	41/153 (26.8)	
FET	16/78 (20.5)	
Cumulative clinical pregnancy per cycle	73/214 (34.1)	
Cumulative live birth per cycle	55/214 (25.7)	

(Note: * = median with IQR of non-normally distributed data. ** = endometriosis stage during the surgical procedure based on the Revised American Fertility Society Classification of Endometriosis, ART = assisted reproductive technology; IVF = in vitro fertilisation; r-FSH = recombinant follicle stimulating hormone; hMG = human menopausal gonadotrophin; r-LH = recombinant luteinising hormone.)

and those who did not were compared to establish the prognostic factors influencing ART outcomes. This study also documented cumulative clinical pregnancy rates per cycle and transfer and miscarriage and multiple gestation rates.

Statistical Analysis
All obtained data were analysed with SPSS statistical software. The mean ± standard deviation (SD) in the present study was computed for the continuous variable. On the other hand, categorical parameters were denoted as proportions. The identification of factors associated with cumulative LBR was performed with a binary logistic regression model. Subsequently, all variables linked to a p<0.25 in univariate analysis were assessed in a multivariate model. The odds ratios (OR) and 95% confidence intervals (CI) were procured from the coefficients of the model.

RESULTS
The present study was conducted from January 2016 to December 2022 and involved 157 patients. A total of 214 cycles and 231 embryo transfers, including fresh and frozen embryo transfers, were performed during the study. Table I lists the clinical and biological characteristics of the patients and cycles. In this study, the cumulative LBR per cycle was 25.7% (n=55), while the cumulative clinical pregnancy rate per cycle was 34.1% (n=73). Nevertheless, one cycle cancellation (0.47%) due to poor response stimulation was observed, seven cycles (3.27%) documented oocyte retrieval failure and ten cycles with no embryo transfer due to poor embryo quality.

The current study performed multiple logistic regression assessments to identify the prognostic factors of ART outcomes in women with endometriosis receiving treatments in the Hospital Sultanah Bahiyah Reproductive Medicine unit. Simple logistic regression was also conducted to screen for critical independent variable (Table II). Independent variables with a 0.25 p-value were selected as potential candidates for the multiple logistic regression. Nevertheless, all variables were analysed during multiple logistic regression as they were considered clinically crucial. The interpretations of the results are listed in Table III.

Patients with 1-year increase in infertility duration recorded 46.7% lesser chances of having live birth (95%CI: 0.33, 0.86, p=0.009) when adjusted for moderate to severe endometriosis and adenomyosis. The results also revealed that females with endometriosis stages III and IV documented 97.8% less live birth probability than women with mild, clinical and unknown types of endometriosis (95%CI: 0.001, 0.39, p=0.009) when adjusted for duration of infertility and the presence of adenomyosis. Patients with adenomyosis had 88.6% less chances of having live birth than patients without adenomyosis (95%CI: 0.013, 0.98, p=0.048) when adjusted for duration of infertility and moderate to severe endometriosis.

DISCUSSION
The current study recorded a good cumulative LBR (25.7%), a similar rate to most reports.[17-19] Factors that significantly affected LBR after IVF-ICSI in women with endometriosis were also identified, namely prolonged infertility durations, moderate to severe endometriosis and the presence of adenomyosis. The other factors, including age, BMI, types of infertility, surgical history, number and interval of surgeries, associated tubal and male factors, presence and size of

Table II: The prognostic factors of ART outcomes in women with endometriosis receiving treatments in the reproductive medicine unit of Hospital Sultanah Bahiyah assessed through simple logistic regression (number of cycles = 214)

Factors	No live birth, n=159 (n, %)	Live birth, n=55 (n, %)	Regression coefficient (b)	Crude OR (95% CI)	Wald statistic	p-value
Age group						
<35 years (n=151)	108 (50.5)	43 (20.1)	0	1		
≥35 years (n=63)	51 (23.8)	12 (5.6)	-0.53	0.59 (0.29, 1.22)	2.04	0.153
BMI (24.36)	24.50 (4.18)*	23.96 (4.36)*	-0.03	0.97 (0.90, 1.04)	0.69	0.40
Infertility type						
Primary (n=184)	140 (65.4)	44 (20.6)	0	1		
Secondary (n=30)	19 (8.9)	11 (5.1)	0.61	1.84 (0.81, 4.17)	2.15	0.142
Number of surgeries						
None (n=12)	10 (4.7)	2 (0.9)	0	1		
One (n=131)	98 (45.8)	33 (15.4)	0.52	1.68 (0.35, 8.08)	0.42	0.515
Two or more (n=71)	51 (23.8)	20 (9.4)	0.67	1.96 (0.39, 9.75)	0.68	0.411
History of surgery						
No (n=12)	10 (4.7)	2 (0.9)	0	1		
Yes (n=202)	149 (69.6)	53 (24.8)	0.58	1.78 (0.38, 8.38)	0.53	0.467
Interval between surgery and ART						
No surgery (n=12)	10 (4.7)	2 (0.9)	0	1		
< 2 years (n=130)	93 (43.5)	37 (17.3)	0.69	1.99 (0.42, 9.52)	0.74	0.389
≥ 2 years (n=72)	56 (26.2)	16 (7.5)	0.83	1.43 (0.28, 7.20)	0.19	0.665
Adenomyosis						
No (n=129)	90 (42.1)	39 (18.2)	0	1		
Yes (n=85)	69 (32.2)	16 (7.5)	-0.63	0.54 (0.28, 1.04)	3.44	0.064
Endometriosis stage						
I and II (n=35)	24 (11.2)	11 (5.1)	0	1		
III and IV (n=149)	111 (51.9)	38 (17.8)	-0.29	0.75 (0.34, 1.67)	0.51	0.476
Clinical (n=12)	10 (4.7)	2 (0.9)	-0.83	0.44 (0.82, 2.34)	0.94	0.333
Unknown (n=18)	14 (6.5)	4 (1.9)	-0.47	0.62 (0.17, 2.34)	0.49	0.483
Associated tubal factor						
No (n=136)	95 (44.4)	41 (19.2)	0	1		
Yes (n=78)	64 (29.9)	14 (6.5)	-0.68	0.51 (0.26, 1.01)	3.79	0.052
Associated male factor						
No (n=172)	126 (58.9)	46 (21.5)	0	1		
Yes (n=42)	33 (15.4)	9 (4.2)	-0.29	0.75 (0.33, 1.68)	0.50	0.481
Presence of endometrioma during cycle						
No (n=139)	103 (48.1)	36 (16.8)	0	1		
Yes (n=75)	56 (26.2)	19 (8.9)	-0.03	0.97 (0.51, 1.85)	0.01	0.928
Size of endometrioma during cycle						
< 3cm (n=55)	41 (54.7)	14 (18.7)	0	1		
≥ 3cm (n=20)	15 (20.0)	5 (6.7)	-0.02	0.98 (0.30, 3.18)	0.002	0.968
COS protocol						
Ultralong agonist (n=150)	112 (52.3)	38 (17.8)	0	1		
Short agonist (n=48)	38 (17.8)	10 (4.7)	-0.25	0.78 (0.35, 1.71)	0.40	0.527
Long agonist (n=16)	9 (4.2)	7 (3.3)	0.83	2.29 (0.80, 6.58)	2.38	0.123
AFC (8.00)	8.00 (5.00)**	9.47 (4.35)**	0.04	1.04 (0.97, 1.12)	1.11	0.292
AFC						
< 5 (n=26)	21 (9.8)	5 (2.3)	0	1		
≥ 5 (n=188)	138 (64.5)	50 (23.4)	0.42	1.52 (0.55, 4.25)	0.64	0.423
Number of mature oocytes	4.00 (4.00)**	5.00 (5.00)**	0.09	1.10 (1.01, 1.21)	4.86	0.028
Fertilisation rate (0.86, 0.19)	0.84 (0.21)**	0.89 (0.16)**	1.48	4.41 (0.76, 25.49)	2.75	0.097

[Note: N=The total sample size, * = mean with standard deviation as the data is normally distributed and ** = median with IQR as data is not normally distributed. Otherwise, all values are in frequency and percentage.]

Table III: The prognostic ART outcome factors of endometriosis patients treated in the reproductive medicine unit of Hospital Sultanah Bahiyah evaluated with multiple logistic regression (n=214 cycles).

Factors	Regression coefficient (b)	Adjusted OR (95% CI)	Wald statistic	p-valuea
Duration of infertility	-0.63	0.533 (0.33, 0.86)	6.81	0.009
Moderate to severe endometriosis (Stage III & IV)	-3.82	0.022 (0.001, 0.39)	6.73	0.009
Presence of adenomyosis	-2.17	0.114 (0.013, 0.98)	3.92	0.048

[Note: a = likelihood ratio test assessed through the backward stepwise method utilising multiple logistic regression.]

endometriomas, COS protocol, AFC, number of mature oocytes, and fertilisation rate, do not influence the cumulative LBR.

A few studies have reported that a longer duration of infertility led to a considerable adverse effect on IVF outcomes among subfertility causes. Conversely, a systematic review and meta-analysis found a negative association between the infertility period and IVF pregnancy rates (OR: 0.99, 95%CI: 0.98-1.00), suggesting that prolonged infertility duration decreases the chances of pregnancy in IVF.[22]
This study demonstrated that a more prolonged infertility period had a negative impact on the LBR in women with endometriosis. Consequently, women diagnosed with endometriosis should seek fertility treatment earlier. Furthermore, in an IVF meta-analysis investigation of endometriosis patients, Barnhart et al., recommended that females diagnosed with endometriosis of any stage should be referred for aggressive infertility treatment early, including IVF, to increase the chances of conception.[19]

A negative association between LBR in females receiving IVF-ICSI and endometriosis severity was noted in this study. The rate of live birth for stage I and II endometriosis (minimal to mild) was 31.4%, whereas stage III and IV endometriosis, it stood at 25.5%. There is a noteworthy decrease in pregnancy rates with stage III and IV endometriosis (OR 0.022), with the majority of the studied population falling into this category. Two meta-analyses indicated that the IVF outcomes of patients with minimal or mild endometriosis were similar to the results of IVF performed for other indications. Nonetheless, the outcomes were inferior in infertile patients with moderate or severe endometriosis (fewer oocytes retrieved, implantation rate, and birth rate).[23,24]Harb et al. also reported that the clinical pregnancy rates and implantation in females diagnosed with stages III and IV endometriosis were significantly reduced by 21%.[24]

Although endometriosis and adenomyosis possess comparable histologic features, including endometrial glands and stroma in abnormal locations, the diseases might affect fertility and pregnancy differently.[25] In a cross-sectional investigation, preoperative MRI was performed on endometriosis patients. The report found that 64.7% of histologically proven endometriosis patients had adenomyosis.[26] In this study, the concomitant adenomyosis presence in endometriosis negatively affected the LBR. The results aligned with a few recent meta-analyses that suggested adenomyosis negatively affects reproductive and obstetric consequences.[27-29]

Recently, the debate on the best ovarian stimulation protocol for patients with endometriosis undergoing ART has garnered significant attention. Ultralong GnRH agonist therapy mechanisms have been studied. The approach diminishes the harmful effects of cytotoxic cytokines and oxidative stress on endometriosis patients' ovaries.[30] The ultralong protocol was primarily employed in this study. Moreover, neither GnRH agonists nor GnRH antagonists COS protocols significantly impacted the LBR results.

Cao et al. compared the effectiveness of three GnRH agonist administration protocols (ultra-long, long, and short) in a meta-analysis investigation.[31] The report noted that the ultra-long protocol improved pregnancy rates in randomised controlled trials (RCTs) more effectively than the long protocol. Conversely, the enhancement was not recorded in non-RCTs. On the other hand, protocols with GnRH antagonists documented an immediate pituitary activity interruption post-administration. Despite being similarly effective as GnRH agonists, GnRH antagonists are more advantageous, offering shorter treatment time, ovarian hyperstimulation syndrome risks and gonadotropin dosage and better patient approval.[32]

A meta-analysis conducted in 2023 indicated that long GnRH agonists and antagonists COS protocols generally yielded similar pregnancy outcomes.[33] Goyri et al., also concluded that ovarian stimulation in endometriosis patients did not differ from other stimulated cycles. Consequently, long pituitary suppression treatments with GnRH agonists were replaced with GnRH antagonists due to their shorter treatment and less gonadotropin doses.[32]

The current study noted that the presence and different sizes of endometrioma had no negative impact on the cumulative LBR during an IVF-ICSI cycle. A previous study also reported no significant variation in LBR after IVF-ICSI in patients with endometrioma compared to control patients.[34] Furthermore, the study revealed that endometrioma surgery did not improve the IVF-ICSI outcomes. In another report, poorer IVF result were recorded in patients with decreased ovarian reserve (DOR) post-endometrioma surgery than patients diagnosed with idiopathic DOR.[35] Moreover, the ESHRE guidelines in 2022 recommended that endometrioma surgical procedures should be performed before IVF only in severe pain cases or to improve access to follicles during oocyte retrieval.[1]

Evidence on endometrioma size influences on ART results remain controversial. For instance, some studies suggested that endometrioma size might be relevant and some cysts of particular diameters could result in harmful effects on ovarian responsiveness to stimulation.[36-38] Conversely, a cohort study that included endometrioma of larger sizes indicated that size did not affect the ART outcomes in women with endometriosis-related infertility.[39] The report suggested that a surgical procedure before IVF-ICSI is not necessary. The findings were supported by current information, which indicated that endometrioma cystectomy before IVF did not improve ART results.[1,34]

The present study had some limitations. Firstly, the retrospective and monocentric design diminished the conclusion strength of this study. The sample size was also relatively small, potentially underestimating the significance of specific factors. Moreover, the study population only included women under 40 and BMI <33kg/m2, thus the data obtained could only be extrapolated to patients with similar profiles.

Original Article

CONCLUSION
The cumulative live birth rate (LBR) in the present study demonstrated a notable decrease linked to extended infertility duration, moderate to severe endometriosis and patients diagnosed with adenomyosis. The findings could hold potential significance in routine clinical practices in advising and guiding couples dealing with endometriosis before opting for ART. Moreover, the results could aid in identifying individuals with diminished IVF-ICSI success prospects, hence preventing unnecessary treatments and allowing exploration of alternative approaches. The present study advocates early and proactive infertility treatment for patients diagnosed with endometriosis. The study is tempered by the small sample size, nevertheless, it could prove valuable for a meta-analytic study.

REFERENCES
1. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: endometriosis. Hum Reprod Open 2022; 2022(2): hoac009.
2. Chapron C, Santulli P, Cabri P. The Pain and Daily Consequences of Living with Endometriosis: A Qualitative Online Survey of Women in China, France and Russia. Journal of Endometriosis and Pelvic Pain Disorders 2015; 7(3): 89-94.
3. Practice Committee of the American Society for Reproductive M. Endometriosis and infertility: a committee opinion. Fertil Steril 2012;98(3): 591-8.
4. Counseller VS, Crenshaw JL, Jr. A clinical and surgical review of endometriosis. Am J Obstet Gynecol 1951; 62(4): 930-42.
5. Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. Epidemiol Rev 1984; 6: 167-91.
6. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 2004;160(8): 784-96.
7. Sangi-Haghpeykar H, Poindexter AN, 3rd. Epidemiology of endometriosis among parous women. Obstet Gynecol 1995; 85(6): 983-92.
8. Arumugam K, Templeton AA. Endometriosis and race. Aust N Z J Obstet Gynaecol 1992; 32(2): 164-5.
9. de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet 2010; 376(9742): 730-8.
10. Al-Azemi M, Bernal AL, Steele J, Gramsbergen I, Barlow D, Kennedy S. Ovarian response to repeated controlled stimulation in in-vitro fertilization cycles in patients with ovarian endometriosis. Hum Reprod 2000; 15(1): 72-5.
11. Boucret L, Bouet PE, Riou J, Legendre G, Delbos L, Hachem HE, et al. Endometriosis Lowers the Cumulative Live Birth Rates in IVF by Decreasing the Number of Embryos but Not Their Quality. J Clin Med 2020; 9(8): 2478.
12. Coccia ME, Rizzello F, Mariani G, Bulletti C, Palagiano A, Scarselli G. Impact of endometriosis on in vitro fertilization and embryo transfer cycles in young women: a stage-dependent interference. Acta Obstet Gynecol Scand 2011; 90(11): 1232-8.
13. Roux P, Perrin J, Mancini J, Agostini A, Boubli L, Courbiere B. Factors associated with a poor prognosis for the IVF-ICSI live birth rate in women with rAFS stage III and IV endometriosis. J Assist Reprod Genet 2017; 34(7): 921-8.
14. Maignien C, Santulli P, Gayet V, Lafay-Pillet MC, Korb D, Bourdon M, et al. Prognostic factors for assisted reproductive technology in women with endometriosis-related infertility. Am J Obstet Gynecol 2017;216(3):280.e1-.e9.
15. Fang Le QK, Yu Sun, Ruizhe Chen, Xinyun Yang, Ning Wang, Huijuan Gao, Fan Jin, Hangying Lou, Yimin Zhu. Prognostic Factors For IVF-ICSI Live Birth Rate in Infertile Women with rAFS Stage III and IV Ovarian Endometriosis. Research Square [PREPRINT] 2022. doi.org/10.21203/rs.3.rs-1318578/v1
16. Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril 2020; 114(6): 1151-7.
17. Polat M, Boynukalın FK, Yaralı I, Esinler I, Yaralı H. Endometriosis is not associated with inferior pregnancy rates in in vitro fertilization: an analysis of 616 patients. Gynecol Obstet Invest 2014; 78(1): 59-64.
18. Muteshi CM, Ohuma EO, Child T, Becker CM. The effect of endometriosis on live birth rate and other reproductive outcomes in ART cycles: a cohort study. Hum Reprod Open 2018; 2018(4): hoy016.
19. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril 2002; 77(6): 1148-55.
20. Amini P, Ramezanali F, Parchehbaf-Kashani M, Maroufizadeh S, Omani-Samani R, Ghaheri A. Factors Associated with In Vitro Fertilization Live Birth Outcome: A Comparison of Different Classification Methods. Int J Fertil Steril 2021; 15(2): 128-34.
21. Kupka MS, Dorn C, Richter O, Felberbaum R, van der Ven H. Impact of reproductive history on in vitro fertilization and intracytoplasmic sperm injection outcome: evidence from the German IVF Registry. Fertil Steril 2003; 80(3): 508-16.
22. van Loendersloot LL, van Wely M, Limpens J, Bossuyt PM, Repping S, van der Veen F. Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis. Hum Reprod Update 2010; 16(6): 577-89.
23. Hamdan M, Omar SZ, Dunselman G, Cheong Y. Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis. Obstet Gynecol 2015; 125(1): 79-88.
24. Harb HM, Gallos ID, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. BJOG 2013; 120(11): 1308-20.
25. Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. Fertil Steril 2023; 119(5): 727-40.
26. Chapron C, Tosti C, Marcellin L, Bourdon M, Lafay-Pillet MC, Millischer AE, et al. Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes. Hum Reprod 2017;3 2(7): 1393-401.
27. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril 2017; 108(3): 483-90.e3.
28. Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Hum Reprod Update 2019; 25(5): 592-632.
29. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod 2014; 29(5): 964-77.
30. Tamura H, Takasaki A, Nakamura Y, Numa F, Sugino N. A pilot study to search possible mechanisms of ultralong gonadotropin-releasing hormone agonist therapy in IVF-ET patients with endometriosis. J Ovarian Res 2014; 7: 100.
31. Cao X, Chang HY, Xu JY, Zheng Y, Xiang YG, Xiao B, et al. The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis. Reprod Biol Endocrinol 2020; 18(1): 16.
32. Goyri E, Kohls G, Garcia-Velasco J. IVF stimulation protocols and outcomes in women with endometriosis. Best Pract Res Clin Obstet Gynaecol 2023; 92: 102429.

33. Kuan KKW, Omoseni S, Tello JA. Comparing ART outcomes in women with endometriosis after GnRH agonist versus GnRH antagonist ovarian stimulation: a systematic review. Ther Adv Endocrinol Metab 2023; 14: 20420188231173325.

34. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update 2015; 21(6): 809-25.

35. Roustan A, Perrin J, Debals-Gonthier M, Paulmyer-Lacroix O, Agostini A, Courbiere B. Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of in vitro fertilization outcome. Hum Reprod 2015; 30(4): 840-7.

36. Somigliana E, Palomino MC, Castiglioni M, Mensi L, Benaglia L, Vercellini P, et al. The impact of endometrioma size on ovarian responsiveness. Reprod Biomed Online 2020; 41(2): 343-8.

37. Coccia ME, Rizzello F, Barone S, Pinelli S, Rapalini E, Parri C, et al. Is there a critical endometrioma size associated with reduced ovarian responsiveness in assisted reproduction techniques? Reprod Biomed Online 2014; 29(2): 259-66.

38. Ferrero S, Scala C, Tafi E, Racca A, Venturini PL, Leone Roberti Maggiore U. Impact of large ovarian endometriomas on the response to superovulation for in vitro fertilization: A retrospective study. Eur J Obstet Gynecol Reprod Biol 2017; 213: 17-21.

39. Bourdon M, Dahan Y, Maignien C, Patrat C, Bordonne C, Marcellin L, et al. Influence of endometrioma size on ART outcomes. Reprod Biomed Online 2022; 45(6): 1237-46.