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# Impact of moderate-to-severe endometriosis on IVF cumulative live birth rate: a retrospective matched cohort study

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## KEY MESSAGE

This matched cohort study explored the impact of moderate-to-severe endometriosis on IVF outcomes compared with other causes of infertility. A significant difference in cumulative live birth rate was not found. These data are reassuring for the counselling of infertile women with endometriosis before IVF.

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## ABSTRACT

**Research question:** Does moderate-to-severe endometriosis have an impact on cumulative live birth rates (cLBR) and IVF outcomes?

**Design:** In this retrospective matched cohort study, women with moderate-to-severe endometriosis undergoing IVF or intracytoplasmic sperm injection treatment from January 2015 to December 2020 were matched 1:2 to women with other causes of infertility (control group). The main outcome was cLBR per cycle and per woman, and secondary outcomes were number of oocytes retrieved and number of mature oocytes, fertilization rate, total number of embryos and usable embryos, implantation rate, clinical pregnancy rate and miscarriage rate per cycle.

**Results:** In total, 195 women with endometriosis were matched with 390 women without endometriosis (323 and 646 cycles, respectively). Women with endometriosis had significantly fewer oocytes retrieved than women in the control group ( $P=0.003$ ) despite higher doses of gonadotropins, but had a similar number of mature oocytes, fertilization rate, and total number of embryos and usable embryos. cLBR per cycle and per woman did not differ significantly between the endometriosis group and the control group (19.8% versus 24.3%,  $P=0.12$ ; 32.3% versus 37.2%,  $P=0.24$ , respectively). In women with endometrioma, a history of cystectomy did not impact cLBR per cycle (28.3% versus 31.9%,  $P=0.68$ ). We did not observe any significant impact of tobacco use in the endometriosis group compared with the control group (16.4% versus 25.9%,  $P=0.13$ ).

**Conclusion:** This matched cohort study did not observe a significant impact of moderate-to-severe endometriosis on cLBR among women undergoing IVF. These data are reassuring for the counselling of infertile women with endometriosis before IVF.

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## KEYWORDS

Endometriosis

IVF

Cumulative live birth rate

## INTRODUCTION

Endometriosis is a benign gynaecologic disease, affecting approximately 10% of women of reproductive age and up to 30–50% of infertile women (Meuleman *et al.*, 2009; Zondervan *et al.*, 2020). Endometriosis is defined as the presence of endometrium-like tissue outside the uterine cavity, mainly in the pelvis. Clinically, endometriosis may be asymptomatic or may manifest with variable symptoms, including pain (dysmenorrhoea, dyspareunia, dyschezia, chronic pelvic pain) and infertility (de Ziegler *et al.*, 2010). Approximately 30% of women with endometriosis are infertile, which is two-fold higher compared with women without endometriosis under 35 years of age (Meuleman *et al.*, 2009).

Pathological mechanisms of endometriosis-related infertility have not been clearly established to date and are multifactorial. Due to inflammation and depending on its location, endometriosis would have a negative impact at several levels on folliculogenesis, ovulation, oocyte quality (Ferrero *et al.*, 2019; Sanchez *et al.*, 2017; Xu *et al.*, 2015), tubal mobility and embryo implantation (Lessey and Kim, 2017). Also, inflammation of the peritoneal fluid could impair sperm functionality (Sáez-Espinosa *et al.*, 2020). Assisted reproductive technology (ART) and surgery are the two tools used to manage endometriosis associated with infertility.

The impact of endometriosis on IVF outcomes is still debated. Several meta-analyses, such as Barnhart *et al.* (2002) and Horton *et al.* (2019), found poorer ART outcomes compared with women without endometriosis or tubal infertility, especially for moderate-to-severe stages of endometriosis [stages III–IV according to the revised American Society for Reproductive Medicine (rASRM) classification]. These results are contested by other authors who reported similar live birth rates between women with endometriosis and women without endometriosis (Barbosa *et al.*, 2014; Dongye *et al.*, 2021; Harb *et al.*, 2013).

The aim of this study was to assess the impact of moderate-to-severe endometriosis on the cumulative live birth rate (cLBR) after IVF by conducting a retrospective matched cohort study.

## MATERIALS AND METHODS

### Study population

A retrospective matched cohort study was undertaken, based on all women aged 18–43 years undergoing IVF or intracytoplasmic sperm injection (ICSI) treatment at the Department of Gynaecology, Obstetric and Reproductive Medicine, La Conception University Hospital, France between January 2015 and December 2020. All women were followed up until May 2022. All women with moderate-to-severe endometriosis (stages III–IV) according to the rASRM classification (American Society for Reproductive Medicine, 1997) were included in the study group. The diagnosis was made by abdomino-pelvic surgery or after magnetic resonance imaging (MRI), as is now commonly accepted (Bazot and Darai, 2017). The control group included women with infertility of any cause except endometriosis. IVF with oocyte donation was a non-inclusion criterion. Exclusion criteria were minimal-to-mild endometriosis (rASRM stages I–II), IVF with sperm donation, and fertility preservation. The endometriosis group was matched with the control group according to age (<30, 30–35, 36–40 or >40 years), body mass index (BMI; <30 or ≥30 kg/m<sup>2</sup>), anti-Müllerian hormone (AMH) concentration (<2, 2–5 or >5 ng/ml), and the exact number of cycles performed at the study centre. Each woman with endometriosis was matched with two controls.

### Ovarian stimulation and IVF

All women underwent one to four ovarian stimulation cycles using four types of protocol: antagonist [daily gonadotropin-releasing hormone (GnRH) antagonist administration from Day 5 of ovarian stimulation], short agonist (daily GnRH agonist administration from Day 2 of ovarian stimulation), long agonist (GnRH agonist administration in the luteal phase of the previous cycle), and ultra-long agonist (intramuscular injection of 3 mg triptoreline per month for at least 3 months before ovarian stimulation). At the study centre, women with endometriosis usually received the ultra-long protocol. Recombinant FSH or FSH and LH gonadotropin were used at doses ranging between 150 IU/day and 450 IU/day, in accordance with BMI, women's age, AMH concentration and antral follicle count.

Follicular growth was monitored by several transvaginal ultrasounds, in addition to

serum oestradiol, progesterone and LH concentrations during ovarian stimulation. Final oocyte maturation was triggered by administering 250 µg of recombinant human chorionic gonadotropin (HCG) when at least three follicles exceeded 17 mm. Oocyte retrieval was performed 36 h after HCG administration. Fertilization was performed with conventional IVF or ICSI using fresh or thawed sperm. Fresh embryo transfers were performed mostly on Day 2 or 3, and some were performed on Day 5. The number of embryos transferred (one or two) was determined by the quality of the embryo(s), the woman's medical history and the couple's choice. The cryopreservation method was vitrification (Irvine Scientific, Santa Ana, CA, USA) in high security straws (Cryo Bio System, L'Aigle, France). The freeze-all strategy could be indicated during ovarian stimulation or after oocyte retrieval, especially if there was risk of ovarian hyperstimulation syndrome. Oral dydrogesterone 30 mg/day was prescribed for luteal phase support after fresh embryo transfer, starting on the day of oocyte retrieval. Frozen and thawed embryo transfers (FET) were performed in natural or gonadotropin-stimulated cycles or artificial cycles under hormone replacement therapy (HRT) with endometrial preparation with exogenous oestrogen and progesterone. Luteal phase support after FET was performed with intravaginal natural progesterone 600 mg/day. Each woman in both groups could undergo zero to five successive FET cycles.

### Outcomes

The primary outcome was cLBR per cycle (including fresh embryo transfers and all FET from that stimulated cycle) and per woman (cLBR per aspiration cycle with at least one live birth per woman). A live birth was defined as a delivery with at least one live born infant. The secondary outcomes were number of oocytes retrieved and number of mature oocytes; fertilization rate, defined as the total number of two-pronuclei-stage oocytes over the total number of mature oocytes; cleavage rate, defined as the number of diploid embryos over the total number of embryos; number of usable embryos, defined as the number of embryos suitable for transfer and vitrification; implantation rate, defined as the total number of gestational sacs over the total number of transferred embryos; clinical pregnancy rate per cycle and miscarriage rate per cycle (Zegers-Hochschild *et al.*, 2017). In women with

endometrioma, cLBR was compared between women with a history of cystectomy, those without a history of cystectomy and those with a history of sclerotherapy (Miquel *et al.*, 2021). A subgroup analysis was also performed to assess the impact of tobacco use on cLBR in the endometriosis group compared with the control group.

### Statistical analysis

Categorical variables were presented as numbers and percentages. Quantitative variables were presented as mean  $\pm$  SD for continuous variables.

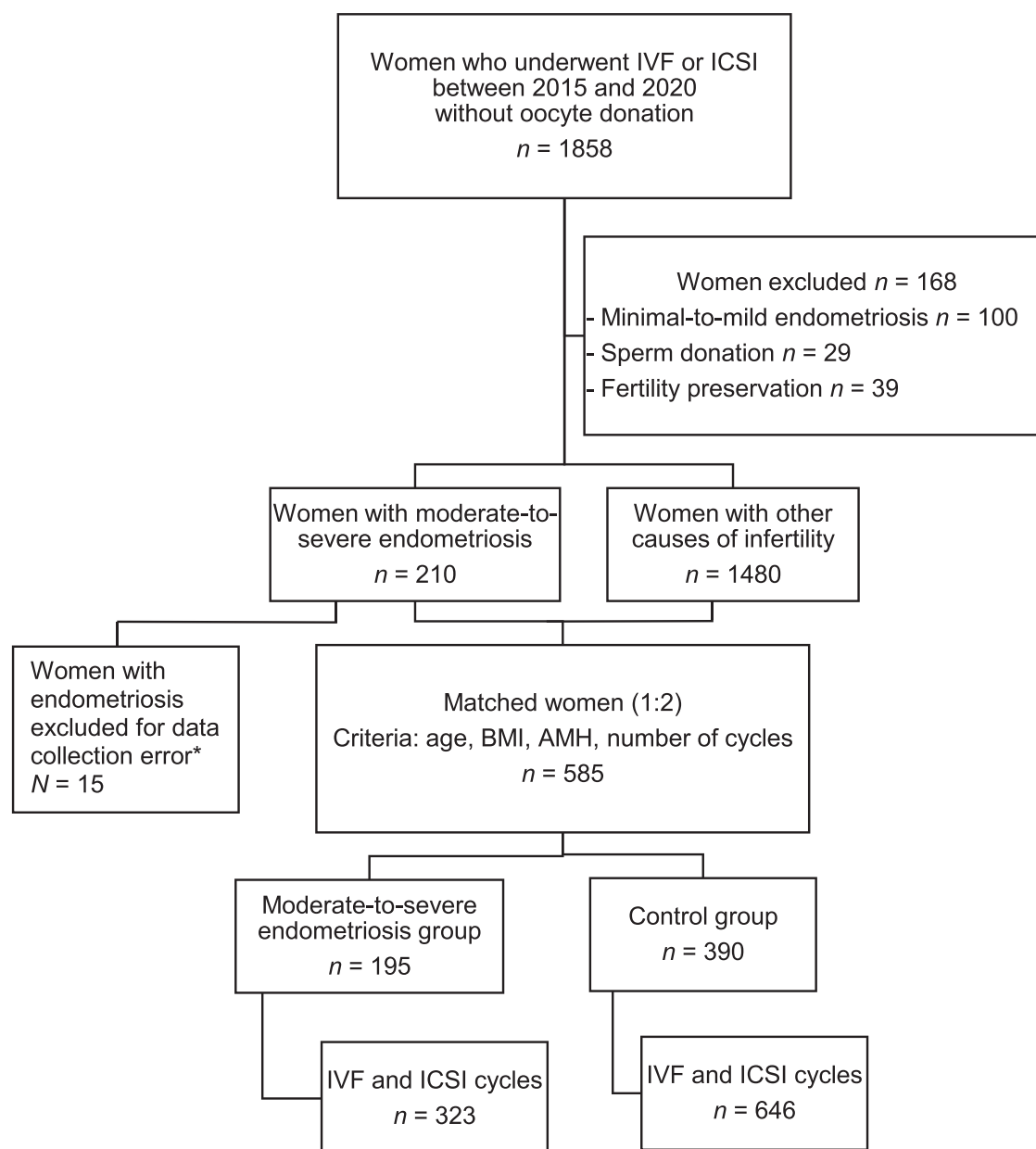
Conditional logistic regression was computed with the four matching variables included in the model as continuous variables. All tests were two-sided and  $P < 0.05$  was considered to indicate significance. SPSS Statistics 20 (IBM Corp., Armonk, NY, USA) and the clogit function from the R package 'survival' were used to perform statistical analyses.

### Ethics statement

This study was approved by the university ethics committee on 8 April 2021 (Reference 2021-04-08-02).

## RESULTS

In total, 585 women were included in this study: 195 women with endometriosis were compared with 390 women without endometriosis, representing 323 and 646 cycles, respectively (FIGURE 1). TABLE 1 summarizes the women's characteristics. In the endometriosis group, mean age was  $33.1 \pm 4.3$  years, mean BMI was  $23.5 \pm 5.0$  kg/m<sup>2</sup>, and mean AMH concentration was  $2.5 \pm 2.1$  ng/ml. The mean number of IVF cycles was  $1.7 \pm 0.9$  for both groups. Baseline characteristics did not differ between the two groups, except for the



**FIGURE 1** Flowchart showing the selection of women and cycles for study inclusion. ICSI, intracytoplasmic sperm injection; BMI, body mass index; AMH, anti-Müllerian hormone. \*Incorrectly entered data relating to the exclusion criteria at initial data extraction and missing cycle data.

**TABLE 1 CLINICAL AND BIOLOGICAL CHARACTERISTICS OF WOMEN IN THE ENDOMETRIOSIS AND MATCHED CONTROL GROUPS**

Characteristic	Endometriosis (n = 195)	Control (n = 390)	P-value
Age (years)	33.1 ± 4.3	33.0 ± 4.5	
BMI (kg/m <sup>2</sup> )	23.5 ± 5.0	24.1 ± 4.8	
Serum AMH (ng/ml)	2.5 ± 2.1	2.5 ± 2.4	
Day 3 serum FSH (IU/l)	7.5 ± 2.7	7.5 ± 2.9	0.70
Duration of infertility (months)	52.1 ± 35.8	53.6 ± 76.3	0.80
Tobacco use	38 (19.5%)	74 (19.0%)	0.88
Type of infertility			0.005
Primary	127 (65.5%) <sup>a</sup>	208 (53.3%)	
Secondary	67 (34.5%) <sup>a</sup>	182 (46.7%)	
Cause of infertility			
Unexplained	0	55 (14.1%)	
Mixed	56 (28.7%)	105 (26.9%)	
Male	0	107 (27.4%)	
Female	139 (71.3%)	123 (31.5%)	
Tubal	0	65/123 (52.8%)	
DOR	0	51/123 (41.5%)	
Other <sup>b</sup>	0	7/123 (5.7 %)	

Data are expressed as mean ± SD or n (%).

<sup>a</sup> Analysed for n total = 194 due to missing data.

<sup>b</sup> Polycystic ovarian syndrome (n = 6), endocrine disorder (n = 1).

AMH, anti-Müllerian hormone; BMI, body mass index; DOR, diminished ovarian reserve.

distribution of primary and secondary infertility. Primary infertility was more common in the endometriosis group (65.5% versus 53.3%,  $P = 0.005$ ).

Among the women with endometriosis, 62.6% (122/195) had deep infiltrating

endometriosis (DIE) with endometrioma, 20.5% (40/195) had DIE without endometrioma, 13.8% (27/195) had endometrioma without DIE, and the information was not available for six women. Regarding women with endometriosis with a surgical history

(n = 139/195), 43.1% had undergone at least one cystectomy for endometrioma (n = 60), and 24.5% had undergone sclerotherapy for endometrioma (n = 34). Women with a history of surgery were younger than women without a history of surgery ( $32.7 \pm 4.3$  versus  $34.1 \pm 4.3$  years,  $P = 0.027$ ), but there was no significant difference in AMH concentration between the groups ( $2.7$  versus  $2.2$  ng/ml,  $P = 0.18$ ).

Regarding ovarian stimulation, 70.9% of women with endometriosis received the ultra-long GnRH agonist protocol, while the antagonist protocol was the most common for the control group (TABLE 2). Women with endometriosis required significantly more gonadotropins ( $3189.5 \pm 1345.8$  versus  $2750.7 \pm 1194.3$  IU,  $P < 0.001$ ). The ICSI rate was significantly higher in the control group compared with the endometriosis group (52.5% versus 31.3%,  $P < 0.001$ ).

IVF outcomes are presented in TABLE 3. The cLBR per cycle (19.8% versus 24.3%,  $P = 0.12$ ) and per woman (32.3% versus 37.2%,  $P = 0.24$ ) did not differ between the endometriosis group and the control group. Women with endometriosis had significantly fewer oocytes retrieved ( $8.3 \pm 5.0$  versus  $9.3 \pm 6.2$ ,  $P = 0.003$ ), but no significant difference in the number of mature oocytes was observed ( $5.9 \pm 3.7$  versus  $6.4 \pm 4.3$ ,  $P = 0.05$ ). No oocytes were retrieved in seven oocyte retrievals in the endometriosis group and two oocyte retrievals in the control group. Maturation rate and fertilization rate were similar in

**TABLE 2 OVARIAN STIMULATION AND IVF CHARACTERISTICS OF THE CYCLES IN THE ENDOMETRIOSIS AND MATCHED CONTROL GROUPS**

Characteristic	Endometriosis (n = 323 cycles)	Control (n = 646 cycles)	P-value
Ovarian stimulation protocol			<0.001
Antagonist	58 (18.0%)	415 (64.2%)	
Long agonist	31 (9.6%)	80 (12.4%)	
Ultra-long agonist	229 (70.9%)	102 (15.8%)	
Short agonist	5 (1.5%)	49 (7.6%)	
Method of fertilization			
IVF	222 (68.7%)	307 (47.5%)	<0.001
ICSI	101 (31.3%)	339 (52.5%)	<0.001
Total gonadotropins administered (IU)	3189.5 ± 1345.8	2750.7 ± 1194.3	<0.001
Total fresh motile sperm count (million)	40.7 ± 46.4	34.7 ± 50.6	0.11
Total thawed motile sperm count (million)	1.1 ± 1.7	2.0 ± 4.7	0.56

Data are expressed as mean ± SD or n (%).

Statistical test: conditional logistic regression with maximum likelihood estimation.

ICSI, intracytoplasmic sperm injection.

**TABLE 3** IVF OUTCOMES OF THE OVARIAN STIMULATION CYCLES IN THE ENDOMETRIOSIS AND MATCHED CONTROL GROUPS

Outcome	Endometriosis (n = 323 cycles)	Control (n = 646 cycles)	P-value
No. of oocytes retrieved	8.3 ± 5.0	9.3 ± 6.2	0.003
No. of retrievals without oocyte(s)	7	2	0.02
No. of metaphase II oocytes	5.9 ± 3.7	6.4 ± 4.3	0.05
Oocyte maturity rate (%)	73 ± 21	72 ± 23	0.24
Fertilization rate (%)	62 ± 21	60 ± 28	0.53
No. of embryos	4.8 ± 3.4	4.8 ± 3.6	0.95
Cleavage rate (%)	76 ± 25	79 ± 23	0.05
No. of fresh ET	237 (73.4)	504 (78.1%)	0.11
No. of fresh embryos transferred per ET	1.8 ± 0.5	1.7 ± 0.5	0.46
No. of embryos vitrified	0.8 ± 1.5	0.8 ± 1.6	0.99
No. of usable embryos	2.1 ± 1.5	2.2 ± 1.6	0.75
No. of FET	116	199	0.11
No. of embryos per FET	1.3	1.3	0.37
Implantation rate (fresh) per cycle (%)	17 ± 31	20 ± 31	0.07
Implantation rate (FET) per cycle (%)	28 ± 40	25 ± 37	0.95
Clinical pregnancy rate per cycle	100 (31)	226 (35)	0.21
Miscarriage rate per cycle	29 (9.0)	51 (7.9)	0.56
cLBR per cycle	64/323 (19.8)	156/643 (24.3)	0.12
cLBR per woman	63/195 (32.3)	144/387 (37.2)	0.24

Data are expressed as mean ± SD or n (%).

Pregnancy outcome was missing for three FET performed in three women from the control group.

ET, embryo transfer; FET, frozen and thawed embryo transfer; cLBR, cumulative live birth rate.

the endometriosis group and the control group: 73% versus 72% ( $P = 0.24$ ) and 62% versus 60% ( $P = 0.53$ ), respectively. Furthermore, the total number of embryos ( $4.8 \pm 3.4$  versus  $4.8 \pm 3.6$ ,  $P = 0.95$ ) and usable embryos ( $2.1 \pm 1.5$  versus  $2.2 \pm 1.6$ ,  $P = 0.75$ ) were similar for both groups. Both groups had similar rates of blastocyst transfer (3.6% versus 3.1%,  $P = 0.68$ ). No significant differences were observed between the two groups in terms of implantation, clinical pregnancy or miscarriage rate per cycle (9% versus 7.9%,  $P = 0.56$ ).

Twenty-seven women (10 women in the endometriosis group and 17 women in the control group) did not return to transfer their remaining vitrified embryos for various reasons (lost to follow-up, separation of the couple, natural conception, or FET planned after the end of the study).

Women with endometriosis with a history of surgery were compared with those without a history of surgery; no significant differences in number of oocytes retrieved ( $8.5 \pm 5.1$  versus  $7.8 \pm 5.0$ ,  $P = 0.26$ ), cLBR

per cycle (21.5% versus 15.8%,  $P = 0.29$ ) and cLBR per woman (34.5% versus 26.8%,  $P = 0.32$ ) were observed. In the endometrioma ± DIE subgroup, cLBR per cycle was 28.3% for women with a history of cystectomy ( $n = 46$ ), 31.9% for women without a history of cystectomy ( $n = 69$ ), and 23.5% for women with a history of sclerotherapy ( $n = 34$ ). There was no significant difference between the three groups ( $P = 0.68$ ). Subgroup analysis of tobacco users found no significant difference in cLBR per cycle between the endometriosis group and the control group (16.4% versus 25.9%,  $P = 0.13$ ).

In the endometriosis group, fresh embryo transfers were compared with FET in women with endometriosis, and no significant difference in live birth rate per transfer was found [19.8% (47/237) versus 14.7% (17/116),  $P = 0.25$ ]. The protocols of the 116 FET were compared, and no significant differences in the clinical pregnancy rate per transfer were found between natural cycles (5/25), ovarian stimulation cycles (2/14) and HRT cycles (10/77) (20% versus 14.3% versus 13%,  $P = 0.67$ ).

## DISCUSSION

Although women with moderate-to-severe endometriosis had a significantly reduced oocyte yield, the chances of clinical pregnancy and live birth did not differ significantly compared with women without endometriosis, after matching for age, BMI, AMH concentration and number of cycles performed.

Several molecular mechanisms have been described to explain the pathophysiology of endometriosis-related infertility. Reactive oxygen species have been described in higher quantities in women with endometriosis, and could alter the processes of maturation, fertilization and embryonic development, particularly by causing DNA damage (Bedaiwy et al., 2002; Szczepańska et al., 2003). Another closely related mechanism is dysregulation of the immune system with increased cytokines in the follicular and peritoneal fluid (Opøien et al., 2013; Shaeib et al., 2015). Both can lead to disruption of cell architecture, including disorganization of the meiotic spindle and remodelling of the extracellular lamina (Da Broi et al., 2014;

*Simopoulou et al., 2021*). As endometriosis is a disease with variable phenotypes and expressions, it is difficult to assess the implication of these mechanisms for natural or ART fertility.

These findings are consistent with the meta-analysis of *Barbosa et al. (2014)*, which included 78 studies, comparing women with and without endometriosis. *Barbosa et al. (2014)* observed a reduced number of oocytes retrieved in women with endometriosis, particularly at advanced stages (rASRM stages III–IV), without a difference in live birth rate. Other systematic reviews and meta-analyses have examined the impact of endometriomas on IVF/ICSI outcomes, and found a reduction in the number of oocytes retrieved, but equivalent pregnancy and live birth rates compared with women without endometriomas (*Alshehre et al., 2021; Hamdan et al., 2015; Yang et al., 2015*). Live birth rates were also equivalent between women with one or more endometriomas and women who had undergone cystectomy for endometriosis (*Hamdan et al., 2015*). The present study did not find a significant difference in cLBR per cycle between women with endometriomas with a history of cystectomy and those without a history of cystectomy. The ovarian reserve of these two subgroups, as assessed by AMH concentration, was not diminished ( $2.1 \pm 1.9$  ng/ml and  $2.0 \pm 1.9$  ng/ml, respectively), which may partially explain these results. In contrast to a previous study by the present authors, sclerotherapy did not appear to improve cLBR; however, the sample size of the previous study was smaller, some of the women who had a history of sclerotherapy also had a history of cystectomy, and the study was not designed to evaluate this technique (*Miquel et al., 2020*).

Boucret et al. compared 155 ICSI cycles performed in women with endometriosis (28 classified as rASRM stages I–II and 127 classified as stages III–IV) with 969 ICSI cycles performed in women without endometriosis (*Boucret et al., 2020*). cLBR were significantly lower in the endometriosis group compared with the control group. Their results could be explained by the fact that the women with endometriosis had a significantly decreased ovarian reserve, related to a frequent history of surgery (50% were classified as rASRM stages III–IV). In their study, women with endometriosis had significantly fewer oocytes, fewer embryos

and fewer very good quality embryos compared with the control group. However, implantation and cLBR per cycle did not differ between the two groups. There was no decrease in the proportion of very good quality embryos in the endometriosis group after multivariate analysis (*Boucret et al., 2020*).

In the present study, despite a reduced number of oocytes retrieved, the number of mature oocytes and fertilization rate were similar in the endometriosis group and the control group.

The oocyte donation model is an interesting approach to investigate oocyte quality. Kamath et al. compared 758 IVF/ICSI cycles of women with endometriosis receiving oocyte donation with 12,856 autologous IVF cycles of women with endometriosis as the only cause of infertility. There was no significant difference in cLBR per cycle after fresh embryo transfer and FET in women receiving oocytes from a donor compared with the autologous oocyte group, even after adjusting for potential confounders. However, no information was provided on the number of donated oocytes and the endometriosis status of the donor women (*Kamath et al., 2022*). In a retrospective study, *Katsoff et al. (2006)* compared implantation and clinical pregnancy rates between a population of 26 women who had received oocyte donations from women with endometriosis and 114 women who had received oocyte donations from women without endometriosis. No significant differences were found between the two groups.

According to the present clinical results and the literature, there appears to be a decrease in the number of oocytes obtained in women with endometriosis without an alteration in oocyte quality. Having studied the database of the Society for Assisted Reproductive Technology, *Senapati et al. (2016)* compared outcomes of women with endometriosis alone ( $n = 12,335$ ) or with other concomitant infertility-related diagnoses ( $n = 21,123$ ) with women with tubal-related infertility ( $n = 22,778$ ), unexplained infertility ( $n = 38,713$ ) and other causes of infertility ( $n = 196,295$ ). They observed a significant reduction in the fertilization rate in women with endometriosis compared with women with tubal-related infertility alone. This study also observed a decreased implantation rate and cLBR per cycle,

and an increased miscarriage rate in the endometriosis combined with other causes of infertility group compared with the three control groups, which was not the case in the endometriosis alone group. No data on other causes of infertility associated with endometriosis or on surgical history were available.

In contrast, the present study did not find any significant differences in implantation or miscarriage rates between the groups. *Juneau et al. (2017)* found that women with endometriosis undergoing IVF do not have increased risk of aneuploidy. In addition, *Bishop et al. (2021)* demonstrated that euploid blastocysts have similar pregnancy outcomes in women with endometriosis compared with women without female infertility in FET cycles.

Some authors explained the decrease in embryo implantation rate and the increase in miscarriage rate by the association with adenomyosis (*Bourdon et al., 2022; Rees et al., 2022*). Unfortunately, it was not possible to consider the impact of adenomyosis in the present study due to missing data.

In a previous study, the present authors showed that tobacco use was an independent prognostic factor, decreasing cLBR per cycle in women with endometriosis (*Roux et al., 2017*). A subgroup analysis was performed to study if tobacco use has a worse impact when associated with endometriosis. The slight difference between the two subgroups of women using tobacco was not significant, possibly due to a lack of power.

Despite the retrospective and monocentric nature of this study, one of its strengths was matching for four potential confounding factors (age, BMI, AMH concentration and number of IVF cycles), which allowed good comparability between the two groups. This study had a good sample size, but it may have lacked the power to show a significant difference. Although clinically relevant concordance criteria were established, matching was performed using wide groups of the four factors, which may have biased the effect of endometriosis on outcomes. However, adjustment for the matching variables may have negated some of the impact. Another limitation of this study was that the control group did not undergo systematic MRI to exclude asymptomatic minimal and mild endometriosis. However, all women in the control group underwent pelvic



specialized sonography before IVF and during ovarian stimulation, which enabled the authors to postulate that moderate-to-severe asymptomatic endometriosis could not be undiagnosed. The majority of women with endometriosis benefited from the ultra-long protocol. The duration of stimulation is usually longer to achieve the trigger criteria with this protocol, which may explain the higher total gonadotropin dose. Ovarian stimulation protocols were not comparable between the two groups, and could have played a role, but recent guidelines from the European Society of Human Reproduction and Embryology did not recommend a specific protocol for endometriosis as no difference in pregnancy or live birth rates has been demonstrated (Becker *et al.*, 2022). The ICSI rate was higher in the control group because of a higher proportion of male infertility. This difference could have favoured the outcomes of the control group.

In conclusion, similar cLBR per cycle and per woman after IVF were observed in women with moderate-to-severe endometriosis compared with women with other causes of infertility. Despite a reduced oocyte yield in women with endometriosis, the total number of embryos transferred and vitrified was equivalent in the endometriosis group and the control group. These results are in accordance with recent meta-analyses, and the data are reassuring for the counselling of infertile women with endometriosis before IVF.

## DATA AVAILABILITY

Data will be made available on request.

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