Factors associated with a poor prognosis for the IVF-ICSI live birth rate in women with rAFS stage III and IV endometriosis

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Abstract

Purpose To assess the factors associated with a poor prognosis for a cumulative IVF live birth rate (LBR) in women with stage III and IV endometriosis according to the revised classification of the American Fertility Society (rAFS).

Methods A retrospective cohort study was conducted between January 1, 2010, and December 31, 2014, in our Reproductive Medicine Center. We analyzed different factors associated with a poor prognosis for a cumulative IVF LBR in women with rAFS stage III and IV endometriosis. A total of 101 patients were included, representing 232 IVF-ICSI cycles and 212 embryo transfers. The primary endpoint was the cumulative LBR per cycle and per patient.

Results The cumulative LBR per cycle was 14.7% ($n = 34$) and that per patient was 31.7% ($n = 32$). The cumulative LBR was significantly decreased by active smoking [$_{adj}$OR = 3.4, 95% CI (1.12–10.60), $p = 0.031$], poor ovarian response (POR) according to the Bologna criteria [$_{adj}$OR = 11.5, 95% CI (1.37–96.83), $p = 0.024$], and rAFS stage IV [$_{adj}$OR = 3.2, 95% CI (1.13–8.95), $p = 0.024$]. The cumulative LBR per women was 59.4% without factors associated with a poor prognosis and 25.6% in the case of one factor, and it decreased to 7.7% in the case of two or three factors ($p < 0.001$).

Conclusion Active smoking, POR according to the Bologna criteria, and rAFS stage IV endometriosis had a negative impact on the IVF-ICSI cumulative LBR for women with rAFS stage III and IV endometriosis. Because smoking dramatically decreases the LBR with endometriosis, stopping smoking before IVF-ICSI should be strongly advised.

Keywords Endometriosis · Infertility · IVF · Pregnancy · Prognosis

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Introduction

Endometriosis is a common gynecological pathology that affects 2 to 10% of women who are of reproductive age in the general population. However, it is found in 40 to 50% of infertile women or women with chronic pelvic pain [1]. The pathogenesis of endometriosis and its associated infertility remains unknown. Miller et al. [2] offered perspectives on the role of immune dysfunction and, more specifically, on the implication of a peritoneal inflammatory microenvironment on hormonal imbalances and oxidative stress, which can lead to poor quality of oocytes and embryos, an altered receptivity of the endometrium and implantation failures. Similarly, Vetvicka et al. [3] hypothesized that extensive inflammation of the microenvironment in patients with endometriosis may lead to a rupture of peritoneal homeostasis and to a decrease in endometrial cell apoptosis and a permissive environment for the progression of the disease.

The classification of the American Fertility Society (AFS) that was established in 1979 and then revised in 1997 (rAFS) is currently the most used. However, this is related to a poor correlation between clinical symptoms in terms of pain or fertility and disease, and it does not account for the involvement of retroperitoneal structures with deeply infiltrating endometriosis (DIE). The Enzian classification system [4] has been developed as a complement for a better description of DIE preoperatively but has a poor level of international acceptance. Its correlation with clinical symptoms has not yet been evaluated. This is why we chose to use the rAFS classification system to define the different stages of endometriosis, and it establishes consensus and a common language for a clearer staging.

At this time, the best approach to cure infertility related to endometriosis is based primarily on clinical guidelines and expert opinions such as the endometriosis guidelines of the European Society for Human Reproduction and Embryology (ESHRE) [5] and the recommendations of the Practice Committee of the American Society for Reproductive Medicine (ASRM) [6]. Operative laparoscopy with adhesiolysis is preferred in rAFS stage I and II endometriosis because it has been shown to improve the spontaneous pregnancy rate [5]. This is still discussed in rAFS stage III and IV endometriosis because the spontaneous pregnancy rate remains very low in these patients and the patients generally require IVF to achieve a pregnancy. There is a lack of randomized controlled trials with a high level of evidence that could provide guidance for the precise management of infertility in women with rAFS stage III and IV endometriosis. The benefit—or lack thereof—of endometriosis surgery before IVF is still being discussed. Some studies have described scoring systems based on patient characteristics with the aim to predict the chances of pregnancy in women with endometriosis regardless of their stages [7, 8]. Nevertheless, no score is available to identify groups with a good or poor prognosis for IVF to further evaluate the benefit/risk for each patient before IVF and provide full information to patients on their chances of treatment success. Finding factors that are associated with a poor prognosis with modifiable criteria could provide opportunities to improve the live birth rate (LBR).

The aim of our study was to assess the factors associated with a poor prognosis for the cumulative LBR in IVF-ICSI in women with rAFS stage III and IV endometriosis.

Materials and methods

This study conformed to the guidelines of the REporting of studies Conducted using Observational Routinely collected Health Data (RECORD) statement.

Population

Between January 1, 2010, and December 31, 2014, data were analyzed retrospectively in the Department of Women, Parents and Children, Clinico-Biological Center for Assisted Reproductive Technology of a University Teaching Hospital (Hôpital La Conception, Marseille, France). From this database, we included all infertile patients who were between 18 and 39 years of age, with rAFS stage III or IV endometriosis diagnosed by laparoscopy after histological confirmation of a surgical specimen [5], with a minimum duration of infertility of 1 year and who had undergone IVF or ICSI.

We excluded all patients who did not consent to participate to the study and patients who did not understand French well enough to give free and informed consent. Patients with comorbidities that could affect live birth after ART, and patients with age ≥ 40 years and/or BMI ≥ 30 kg/m^2 were excluded because these conditions are potential confounders in the study.

Concerning the clinical characteristics of patients, the criteria examined were as follows: age, body mass index (BMI), active smoking, the type and duration of infertility (primary or secondary), and the presence or absence of other causes of infertility (uterine anomalies, male factor infertility). Active smoking was defined by smoking behavior including one cigarette. For endometriosis, we assessed the history of endometriosis surgery before assisted reproductive technology (ART), the history of endometrioma surgery (cystectomy/drainage /electrocoagulation/sclerotherapy), the presence of an endometrioma at the time of IVF, and the presence of deep infiltrating endometriosis (DIE).

Concerning ovarian reserve markers, we assessed anti-müllerian hormon (AMH) with a Beckman-Coulter kit (ng/mL), FSH (UI/L), and the antral follicle count by ultrasonography. A poor ovarian response (POR) was defined by the Bologna criteria [9]. At least two of the following three features had to be present to define a patient as a poor responder: advanced maternal age greater than or equal to 40 years or any other risk factor for POR, a previous POR (≤3 oocytes with a conventional stimulation protocol), and an abnormal ovarian reserve test (antral follicle count <5–7 follicles or AMH < 0.5–1.1 ng/mL). Two episodes of POR after maximal stimulation were sufficient to define a patient as a poor responder in the absence of advanced maternal age or abnormal ovarian reserve test. Risk factors for decreased ovarian reserve included tobacco use, family history of POR, genetic anomalies (Turner's syndrome, FMR1), presence of endometrioma, history of ovarian surgery, and history of chemotherapy or radiotherapy.

For the IVF protocols, we assessed the type of ART (IVF or ICSI), the rank of the IVF attempt, the controlled ovarian stimulation (COS) protocol, the total dose of gonadotropin, the biological and ultrasonographic parameters of the

triggering (endometrial thickness, estradiol level), the number of retrieved oocytes, the fertilization rate, the number of fresh embryos transferred, and the number of frozen-thawed embryos transferred.

Treatment protocol

COS protocols were recorded as the long protocol (GnRH agonist administration in the luteal phase of the previous cycle), short protocol (daily GnRH agonist administration since the first day of the IVF cycle), or antagonist protocol (daily GnRH antagonist administration from Day 5). Patients received an administration of GnRH agonists (Decapeptyl® LP) for 3 to 6 months prior to each IVF or ICSI cycle. We did not use oral contraceptives to program the start of the cycle. We used recombinant FSH and second-line hMG in cases of poor follicular recruitment or when the estradiol level did not rise sufficiently during COS. The initial daily dose was 150 IU/day, and the dose was adjusted according to BMI, patient age, day 3 FSH value, size and number of follicles, and estradiol level. The IVF cycle's follow-up consisted of transvaginal ultrasound and both serum estradiol and LH measurements. The dose of gonadotropin was then adjusted at day 8 of stimulation according to the ovarian response. Human chorionic gonadotropin (HCG) 10,000 IU was injected intramuscularly, or recombinant-derived r-HCG was injected subcutaneously when at least three follicles reached a mean diameter of 16 mm. Then, patients underwent oocyte retrieval under local or general anesthesia via a transvaginal ultrasound-guided puncture of follicles 36 h after HCG administration. The luteal phase was supported by daily progesterone tablets starting on the day of oocyte retrieval until a pregnancy blood test was executed. Embryo transfer was mostly performed 48–72 h after oocyte retrieval under ultrasound guidance. All patients included in this study used all their embryos except after obtaining a live birth or after failure at the end of their ART management. Endometrial preparation for frozen-thawed embryo transfer (FET) consisted of an artificial cycle with 4 to 6 mg day^{-1} of oral estradiol with prior pituitary suppression using long-acting agonists. Progesterone (600 mg per day) was administered when the endometrium reached at least 8 mm with 2–3 day ET performed 5 days later.

Pregnancy was initially diagnosed by a positive level of plasma HCG on day 14 after ET. Then, we collected the following data: clinical pregnancy defined by the presence of an embryo with cardiac activity on ultrasound at 8 weeks, ectopic pregnancy, singleton or twins, early miscarriage defined as fetal loss before 10 weeks, late miscarriage defined as fetal loss between 10 and 22 weeks, the occurrence of complications during pregnancy, gestational age at delivery, and type of delivery (vaginal delivery, cesarean).

Outcome measure

The primary study endpoint was the cumulative LBR per IVF-ICSI cycle and per patient. For each cycle, we calculated the cumulative LBR after fresh and frozen ET.

The secondary endpoints were the clinical pregnancy rates per cycle and per patient, as defined by the presence of an embryo with cardiac activity on ultrasound at 8 weeks, a positive level of plasma HCG on day 14 after ET, the miscarriage rate, and any complications during pregnancy.

Statistical analysis

The mean ± standard deviation (SD) was computed for every continuous variable. Categorical variables were expressed as proportions.

A binary logistic regression model was used to identify factors associated with cumulated LBR per patient. All factors associated with a p value <0.2 in univariate analysis were then tested in a multivariate model.

All statistical analyses were two-tailed and considered statistically significant when the p value <0.05. The statistical analyses were performed using SPSS PAWS Statistics 18.0 (IBM Inc., New York, USA).

Results

A total of 101 patients were included from January 1, 2010, to December 31, 2014, with a total of 232 cycles, 270 attempts and 212 ET, including fresh and frozen ET. Clinical and biological characteristics of patients and cycles are summarized in Table 1. The cumulative LBR per cycle was 14.7% ($n = 34$), and the cumulative pregnancy rate per cycle was 19.0% ($n = 44$). The cumulative LBR per patient was 31.7% ($n = 32$), and the cumulative pregnancy rate per patient was 38.6% ($n = 39$).

There were 40 patients for whom there was cycle cancelation (17%) with 32 non-response cancelations, 4 cancelations due to patients being lost to follow-up, 2 hyper-responses, and 2 failures of hormonal blocking. There were 53 patients for whom there was no embryo transfer (20%).

Univariate analysis

Data related to the univariate analysis are summarized in Table 2.

With univariate analysis, the cumulated LBR per patient was significantly decreased by active smoking ($p = 0.03$), rAFS stage 4 ($p = 0.049$), and a POR according to the Bologna criteria ($p = 0.002$). Similar results were found for the cumulative pregnancy rate per cycle. The presence of DIE

Table 1 Characteristics of the study population and IVF cycle (total population = 101 and number of cycles = 232)

	N/total (%) unless shown otherwise
Age on the day of IVF (mean ± SD)	31 ± 4
<35 years	82/101 (81%)
35–39 years	19/101 (19%)
Duration of infertility (mean ± SD)	3 ± 2
<3 years	43/101 (43%)
≥3 years	58/101 (57%)
Previous pregnancy	
No	84/101 (83%)
Yes	17/101 (17%)
Infertility	
Primary	87/101 (86%)
Secondary	14/101 (14%)
Active smoking	
No	68/101 (67%)
Yes	33/101 (33%)
AMH (ng/mL) (mean ± SD)	2.7 ± 2
Poor ovarian response (POR) according to Bologna criteria	
No	79/101 (78%)
Yes	22/101 (22%)
Antral follicle count (mean ± SD)	11 ± 6
rAFS endometriosis stages	
3	56/101 (55%)
4	45/101 (45%)
Endometrioma	84/101 (83%)
Endometrioma surgery	55/101 (55%)
Endometrioma cystectomy	45/101 (45%)
Sclerotherapy	10/101 (10%)
Deep infiltrating endometriosis (DIE)	92/101 (91%)
History of DIE surgery	57/101 (56%)
Uterine anomalies	
No	95/101 (94%)
Yes	6/101 (6%)
Male factor infertility	
No	75/101 (74%)
Yes	26/101 (26%)
Type of ART procedure	
IVF	192/232 (83%)
ICSI	40/232 (17%)
Rank of the IVF attempt	
1 cycle	97/232 (42%)
2 cycles	71/232 (31%)
3 cycles	40/232 (17%)
4 cycles	24/232 (10%)
Presence of endometrioma during the cycle	105/232 (45%)
Controlled ovarian stimulation protocols	
Long agonist	184/232 (79%)
Short agonist	40/232 (17%)

Table 1 (continued)

	N/total (%) unless shown otherwise
Antagonist	8/232 (4%)
Use only recombinant FSH	94/232 (41%)
Use FSH + hMG	138/232 (59%)
Total dose of gonadotropin (mean ± SD)	2344 ± 1214
Estradiol level (mean ± SD)	2474 ± 1658
Type 1 of endometrium	118/232 (51%)
Endometrial thickness	
>7 mm	198/232 (85%)
≤7 mm	34/232 (15%)
Number of retrieved oocytes (mean ± SD)	5 ± 5
≤3	65/232 (28%)
>3	167/232 (72%)
Number of oocyte retrievals without oocyte	1/232 (0.4%)
Cycle cancelation	40/232 (17%)
Fertilization rate (mean ± SD)	58 ± 39
Number of formed embryos (mean ± SD)	4 ± 3
Embryo transfer (n = 212)	
1 embryo transferred	75/212 (35%)
2 embryos transferred	135/212 (64%)
3 embryos transferred	2/212 (1%)
Number of fresh embryos transferred	185/212 (87%)
Number of frozen-thawed embryos transferred	27/212 (13%)
Day of transfer	
Day 2	166/212 (78%)
Day 3	46/212 (22%)

SD standard deviation

or endometrioma did not influence the cumulative LBR per patient ($p = 0.818$ and $p = 0.297$, respectively).

Concerning active smoking, 15 women smoked more than 10 cigarettes per day, and 18 women smoked fewer than 10 cigarettes per day. There was no difference between these groups in terms of cumulated LBR.

Multivariate analysis

Data related to the multivariate analysis are shown in Table 2. We found an independent significant relationship with poor prognosis on the cumulative LBR per patient for active smoking ($p = 0.031$), POR according to the Bologna criteria ($p = 0.024$), and rAFS stage IV ($p = 0.028$). Active smoking, POR and rAFS stage IV endometriosis were therefore independent risk factors for the poor prognosis of cumulative LBR per patient after adjusting for the specific population of women with rAFS stage III and IV endometriosis. These variables allow the chances to have an IVF live birth to be assayed, and the results are shown in Table 3.

Table 2 Factors associated with poor prognosis of cumulated live birth rate after IVF in patients with endometriosis rAFS III/IV (n = 101)

Prognosis factors	No live birth	≥1 live birth	P value	Adjusted odds ratio[a]	95% CI	P value
Duration of infertility, mean (SD)	3.3 (2.0)	3.6 (2.8)	P = 0.479	NE		
No prior pregnancy	87.0%	75.0%	P = 0.135	3.3	0.97–11.49	P = 0.056
Active smoking	39.1%	18.8%	**P = 0.042**	3.4	1.12–10.60	**P = 0.031**
POR (Bologna criteria)	30.4%	3.1%	**P = 0.002**	11.5	1.37–96.83	**P = 0.024**
Stage IV rAFS	52.2%	28.1%	**P = 0.024**	3.2	1.13–8.95	**P = 0.028**
Deep Infiltrating Endometriosis	92.8%	87.5%	P = 0.459	NE		
Endometrioma	85.5%	78.1%	P = 0.356	NE		

CI confidence interval, *NE* variable not entered in the multivariate model, *SD* standard deviation, *POR* poor ovarian response, *rAFS* revised classification of the American Fertility Society

[a] Multivariate binary logistic regression analysis

Pregnancy outcome

Twenty-one patients had complications during pregnancy (53.8% of clinical pregnancy). There were eight threatened preterm births, three episodes of metrorrhagia on placenta previa, three cases of gestational diabetes, two ovarian hyperstimulation syndromes during pregnancy, one premature ruptures of membranes, two intrauterine growth restrictions, one fetal malformation, and one endometrioma hemorrhagic rupture treated by laparoscopy for hemoperitoneum with pregnancy loss.

Discussion

In our study, we had a good cumulative pregnancy rate and LBR in IVF. This is similar to the study of Polat et al. (2014) [10], who concluded that women with endometriosis, regardless of the stage of the disease and its extent, had an IVF pregnancy rate and an IVF LBR equivalent to those of women with tubal infertility without endometriosis. We found three factors that significantly affected LBR after IVF-ICSI in women with rAFS stage III and IV endometriosis: active smoking, POR, and rAFS stage IV. Our results are concordant with the published data. POR and active smoking are independent known risk factors for poor results in infertile women, and

Table 3 Assessment of the chances to have an IVF live birth per patients with endometriosis rAFS stages III and IV

Number of factors associated with poor prognosis	% Cumulated LBR (n = 32)
0	59.4 (n = 19)
1	25.6 (n = 11)
2 or 3	7.7 (n = 2)

active smoking remains a risk factor for a poor prognosis for cumulative LBR per patient after multivariate analysis with POR adjustment.

Active smoking impairs every stage of the reproductive process, from folliculogenesis to embryonic development [11]. According to our knowledge, there are no studies showing active smoking as significantly associated with a decrease in the cumulative LBR in the specific population of women with rAFS stage III and IV endometriosis. Concerning endometriosis, several studies have established scores based on patient characteristics attempting to predict their spontaneous or ART pregnancy rate, but the preexisting scores did not consider smoking to be a factor associated with a poor prognosis for the cumulated LBR. Our study demonstrated that active smoking had a negative impact on the LBR for women with rAFS stage III and IV endometriosis. Because smoking decreases the LBR dramatically in endometriosis, stopping smoking before IVF-ICSI should be strongly advised.

POR, according to the Bologna criteria [9], was one of the three main factors associated with a poor prognosis for cumulative LBR per patient. Unlike in most studies, the Bologna criteria were chosen, not just the AMH or antral follicle count, because they provide a clearer and reproducible definition of POR. Polyzos et al. [12] showed a very low LBR in patients with POR, regardless of their age and the treatment protocol used. Thus, it appears that age could not be a strong prognostic success factor of IVF-ICSI for POR. These results are contradictory to those of numerous previous studies, which demonstrated that age is a strong determinant of the IVF pregnancy rate [7, 8, 13]. Santulli et al. [14] demonstrated that age > 32 years was an important risk factor for endometriosis-related infertility (OR = 1.9; 95% CI 1.4–2.4). Therefore, the contradictions between studies do not necessarily involve contradictory results but may reflect the diversity in the definition of POR, which is why it is important to find a consensus on this definition with the Bologna criteria.

rAFS endometriosis staging does not allow prediction of the clinical outcomes of endometriosis in terms of pain or infertility. However, Pop-Trajkovic et al. [15] found a negative correlation between the LBR in IVF-ICSI and the severity of endometriosis. Moreover, Shebl et al. [16] showed that endometriosis rAFS stage IV was associated with significantly worse-quality oocytes than stages I-III ($p < 0.01$).

Our results are aligned with previous studies that established a prognostic score for the pregnancy rate after IVF-ICSI, in the context of endometriosis, such as the nomogram of Ballester et al. [8]. The authors studied women with endometriosis, regardless of its severity. Their primary endpoint was the pregnancy rate and not the LBR. We chose the cumulated LBR because even if it remains controversial, several articles have shown that the miscarriage rate was higher for women with endometriosis [17]. Moreover, according to Maheshwari et al. [18] and Malizia et al. [19], the cumulative LBR better reflects patients' expectations: giving birth rather than being pregnant. Concerning DIE surgery, several articles aimed to evaluate the benefits of surgery on fertility outcomes in women with DIE and, in particular, on colorectal endometriosis. There appears to be a potential benefit of intestinal surgery on fertility in spontaneous pregnancies and post-ART, particularly in patients with rAFS stage IV endometriosis who are most affected [20]. However, it is not clear whether the surgery should be performed as a first-line surgery or should be limited to cases in which ART fails [21]. Cohen et al. (2016) [22] advised starting with a first-line IVF in the case of women aged 35 years or older, in the case of associated male infertility or tubal obstruction, or if the ovarian reserve is reduced. Similarly, it is universally clear that management must be multidisciplinary and minimally invasive. The debate persists between a complete surgery associated with a higher risk of complications and a minimally invasive surgery associated with an increased risk of recurrence if this resection is partial [23]. The articles of Soriano et al. (2016) [24] showed a surgery benefit for infertile patients with rAFS stage III and IV endometriosis and with repeated IVF failures. This benefice is higher for patients who are younger, have a normal ovarian reserve, and do not have uterine anomalies. In our cohort, 90% of the women had a DIE because we included only patients with rAFS stage III and IV endometriosis. Therefore, the presence of DIE or DIE surgery did not appear to be a significant prognostic factor for the cumulated LBR.

Concerning endometrioma surgery, in our study, we found no evidence of a negative impact from the presence of endometrioma during an IVF-ICSI cycle on the cumulated LBR. In the meta-analysis of Hamdan et al. [25], there was no significant difference in LBR after IVF-ICSI in patients with endometrioma compared to control patients, and the endometrioma surgery did not improve the outcome of treatment with IVF-ICSI compared to patients who did not undergo surgery. Moreover, Roustan et al. [26] showed that a

diminished ovarian reserve after endometrioma cystectomy involved a worse IVF prognosis than an idiopathic diminished ovarian reserve. Finally, the ESHRE guidelines [5] advise that endometrioma cystectomies should be performed before IVF only in cases of severe pain or to improve access to follicles during oocyte retrieval.

Concerning the down-regulation by a GnRH agonist before an IVF cycle, the Cochrane review of Sallam et al. (2006) [27] demonstrated that long-term pituitary down-regulation with a GnRH agonist for 3 to 6 months before IVF or ICSI improves the clinical pregnancy rates by fourfold in patients with endometriosis. The study of Van Der Houwen et al. (2014a) [28] found a favorable but non-significant effect on ongoing pregnancies only after including transfers of frozen embryos. Although the mechanism of action is not yet clearly explained, in our study, all patients benefited from the administration of GnRH agonists for 3 months prior to IVF or ICSI.

In recent analyses, the decrease in fertility with endometriosis may be at least partially related to the epigenetic profile of the eutopic endometrium versus the ectopic endometrium. Borghese et al. (2017) [29] found an important genetic component in endometriosis with an estimated heritability of approximately 50%. This may demonstrate an unfavorable cross-talk between endometrial cells and immune cells. The study by Lagana et al. (2016) [30] referred to the notion of a fine-tuned microenvironment in which innate and adaptive immunity create an equilibrium that allows the physiological processes of reproduction. This could constitute new therapeutic targets in the medical treatment of endometriosis.

Our patients started directly with the IVF or ICSI cycle, contrary to the study of Van Der Houwen et al. (2014b) [31], who showed that patients with rAFS stage III and IV endometriosis should have an intrauterine insemination (IUI) with ovarian stimulation before IVF with a maximum of 3 cycles because it is less expensive and less radical. Nevertheless, most of our patients did not have a patent Fallopian tube, but this was considered in our study because doing so did not waste a lot of time, especially because our cohort of patients was young.

There are some limits to our study. The retrospective and monocentric case control design lowers the power of the conclusions. Then, the size of the sample is relatively small and potentially underestimates the significance of certain factors. As a consequence, a larger series would be needed to confirm these findings, and validation in an independent second sample of similar patients would be necessary to assay prognostic factors. Moreover, study population is represented by women under 40, non-obese, with cleavage stage embryo transfer day 2 or 3, so the data from this study can only be extrapolated to patients with a similar profile.

In conclusion, our study provided accurate information regarding IVF-ICSI success for women with rAFS III and IV endometriosis and provided data estimating the cumulative LBR using three criteria: active smoking, POR according to

Bologna criteria, and rAFS stage IV endometriosis. Our results could be used in clinical practice to inform and counsel couples before ART for AFS III and IV endometriosis. Stopping smoking should be especially recommended before ART for these patients. Our results could also facilitate the identification of patients with poor chances of success with IVF-ICSI, avoiding unnecessary treatments and allowing the guidance of couples regarding alternative approaches. A larger series and a multicentric approach are needed to confirm these findings and develop a score that includes all of the prognostic factors for endometriosis. An independent validation cohort would also be necessary to validate a prognostic score with the criteria defined in our study.

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