Prognostic Factors For IVF-ICSI Live Birth Rate in Infertile Women with rAFS Stage Ⅲ and Ⅳ Ovarian Endometriosis

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Abstract

Purpose

To investigate whether the assisted reproductive technology (ART) outcome differed amongst women with primary and recurrent endometriomas and to identify prognostic factors for a poor cumulative live birth rate (cLBR) in women with severe endometriosis by a retrospective cohort analysis.

Methods

A total of 836 patients with stage Ⅲ and Ⅳ ovarian endometriosis were included; of which 734 women without and 102 with recurrent endometrioma underwent 1048 ART cycles. The main outcome measures were cumulative clinical pregnancy rate (cPR) and cLBR per cycle. Prognostic factors of ART outcome were identified by comparing women who became pregnant with those who did not, using univariate and adjusted multiple logistic regression models.

Results

In all, 549 (65.67%) women became pregnant and 507 (60.65%) had a live birth. The cumulative cPR and LBR per cycle were 54.20% and 48.38%, respectively. In the recurrent group, the antral follicle count (AFC) and number of retrieved oocytes were lower than for women with primary endometriomas. However, the cLBR were similar between the two groups. Further, after multivariate analysis, ages ≥35 y and time interval ≥2 y between surgery and ART were independent factors associated with lower cLBR in patients with severe endometriosis. Number of surgeries ≥2 and lower AFC were also associated with negative ART outcomes.

Conclusion

An advanced maternal age, an altered ovarian reserve, number of surgeries, and/or longer interval between surgery and ART had a negative impact on ART cLBR for infertile women with rAFS stage Ⅲ and Ⅳ ovarian endometriosis.

Retrospective trial registration number

: IRB-20210319-R, date of registration: 4.10.2021

Introduction

Endometriosis is a chronic benign gynecological disease that is defined as the presence of endometrial gland and stromal tissue outside the uterine cavity. It is observed primarily in patients of reproductive age, and its prevalence is estimated to be 5–10%, or 25–50% of infertile women [1–3]. Classically, the disease is categorized as peritoneal, ovarian, or deep infiltrating endometriosis (DIE) [4]. Ovarian endometriosis is the most common type, accounting for 17–44% of all endometrioses, and is often associated with infertility [5, 6]. Nowadays, treatment options for ovarian endometriosis include surgical treatment, medical treatment, conservative management, or assisted reproduction technique (ART) in cases of associated infertility [7]. Optimal management of endometrioma before an ART cycle, however, is still controversial.

Surgical management has been considered the gold standard treatment for ovarian endometrioma, but researchers have reported conflicting results regarding the benefit of ovarian cystectomy and reproductive outcomes. Studies have demonstrated that surgical treatment of endometriomas in infertile women can improve spontaneous pregnancy rates to between 20% and 60% [8–10]. Other studies have found ovulation rates to be lower in ovaries associated with an unoperated endometrioma as compared to the contralateral healthy ovary [11]. Additionally, in the cortical layer of ovaries with untreated endometriomas, a decreased follicular density was detected compared to contralateral healthy ovaries [12]. However, there remains a concern that ovarian surgery for endometriomas impairs ovarian reserve by damaging healthy ovarian tissue, thus resulting in poorer fertility outcomes. Decreased number of collected oocytes and serum levels of anti-Mullerian hormone (AMH) have been found in ovaries post-surgery [13, 14]. Moreover, the recurrence rate following surgical endometriomas remains high at between 6% and 67% [15–17], even for those who receive postoperative medical therapy. Except for a more careful consideration of the decision to proceed with surgery, current guidelines on the management of endometrioma do not give specific indications for treatment of any recurrence.

The effect of endometriosis on fertility may be varied according to the stage, which is classified by the revised American Fertility Society (rAFS). In mild endometriotic disease (Stage I/Ⅱ), the postoperative clinical pregnancy rate has been quoted as almost double that of diagnostic laparoscopy alone, from 17.7–30.7% [7]. However, a worsening stage of the disease appears to be correlated with reduced fertility. Studies reveal a significant reduction in clinical pregnancies and live birth rate (LBR) in patients with severe endometriosis undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) treatment [18, 19]. However, there is still a lack of evidence to identify a good or poor prognosis for IVF/ICSI to further evaluate the risk for patients before ART, and to be able to fully advise patients on their chances of treatment success, particularly for infertile women with rAFS stage Ⅲ and Ⅳ endometriosis. Hence, the aim of the present study was firstly to evaluate ART outcome in infertile women with rAFS stage Ⅲ and Ⅳ ovarian endometriosis. Secondly, we sought to answer the question of whether postoperative recurrent endometriomas impact on ART outcome, by comparing ART outcome between women with primary and recurrent endometriomas after histological analysis. Lastly, the risk factors associated with a poor prognosis for the cumulative LBR (cLBR) were explored in IVF-ICSI women with rAFS stage Ⅲ and Ⅳ ovarian endometriosis.

Materials And Methods

Ethical approval

This study was approved by the Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine (IRB-20210319-R). Written informed consent was obtained from all participants.

Population

Between January 1, 2014, and July 31, 2018, data were analyzed retrospectively in the Center of Reproductive Medicine, Zhejiang University School of Medicine Women's Hospital. From this database, we included all infertile patients who were between 20 and 39 years of age, with a minimum duration of infertility of 1 y and who had undergone IVF or ICSI treatment. Endometrial, tubal factor, and male factor infertility were included in this study. Patients with comorbidities that could affect LBR after ART were excluded, such as patients with age ≥40 y, body mass index (BMI) ≥30 kg/m^2, and/or risk factors for decreased ovarian reserve including tobacco use, family history of premature ovarian failure, genetic anomalies, history of other ovarian surgery, and history of chemotherapy or radiotherapy.

The study population consisted of 836 patients with stage Ⅲ and Ⅳ endometriosis which comprised 734 women without and 102 with recurrent endometrioma. An endometrioma (the endometriosis phenotype being examined) was defined as the visualization of an ovarian cyst and associated adenomyosis diagnosed based on transvaginal ultrasound examination or magnetic resonance imaging (MRI). In all clinics, the presence of cysts was confirmed on at least two separate examinations performed at least one month apart. The diagnosis was confirmed by histological proof of the ovarian endometriosis after surgery, and without DIE lesions. Women with a history of a prior endometrioma excision were included in the recurrent endometrioma group with a mean cyst diameter <4 cm.

For each patient, personal history data and results of fertility investigations were collected before ART treatment. The following data were recorded: age, height, weight, BMI, parity, gravidity, duration of infertility; and cycle day-3 levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol; antral follicle count (AFC) by ultrasonography, semen analysis as per the World Health Organization manual, and the presence of adenomyosis at the time of IVF. AFC is the sum of the number of antral follicles in both ovaries as observed with transvaginal ultrasonography during the early-follicular phase. Antral follicles were defined as those measuring 2–10 mm in mean diameter in the greatest two-dimensional plane across the surface of the ovary [20]. For women with stage Ⅲ and Ⅳ ovarian endometriosis, we further assessed the history of endometriosis surgery before ART, recurrent endometrioma during the IVF, therapy of GnRH-a (3–6 months) after surgery, and time interval between surgery and ART.

For the ART protocols, we assessed the type of IVF or ICSI, the rank of the IVF attempt, the controlled ovarian stimulation (COS) protocol, the total dose of gonadotropin, the number of retrieved oocytes, the fertilization rate, the number of fresh embryos transferred, and the number of frozen-thawed embryos

transferred. COS parameters documented for all patients included duration of ovarian stimulation (d), total dose of gonadotropins (IU), and peak estradiol level (pmol/L) on human chorionic gonadotrophin (hCG) trigger day, along with the number of oocytes retrieved.

Treatment protocol

Patients were stimulated either using an ultra-long or long gonadotropin-releasing hormone (GnRH) agonist (GnRH-a), a short agonist, or an antagonist (GnRH-A) protocol. For all the protocols, the dosage of r-FSH was adjusted; in addition, human menopausal gonadotrophin (hMG), or r-LH, or GH was added according to the ovarian response as evaluated by transvaginal ultrasonography and serum hormone levels. Transvaginal oocyte retrieval was performed 34–36 h after the hCG injection.

GnRH-a ultra-long protocol: The patients in the ultra-long protocol group underwent down-regulation by receiving 3.75 mg GnRH-a (3.75 mg Leuprorelin Acetate Microspheres; LiZHu, China) on days 2–3 of the menstrual cycle. Twenty-eight days later, 3.75 mg Leuprorelin was administered again, lasting for 28–35 days until pituitary down-regulation was confirmed. Complete pituitary suppression was confirmed by a serum E2 level <50 pg/mL and serum FSH and LH levels <5 IU/L. Recombinant FSH (rFSH; Gonal-F or Puregon; Merck Serono, France) and/or hMG (LiZHu, China) were used at doses ranging between 100 IU/d and 300 IU/d in accordance with body mass index, patient age and size, and number of follicles. If two or more follicles reached a maximum diameter of 19 mm, 250 μg of hCG (Ovidrel; Merck Serono, France) was administered.

GnRH-a long-protocol: GnRH agonist (Leuprorelin) 0.1 mg by subcutaneous injection was administered daily for 12–14 days starting from the mid-luteal phase of the menstrual cycle; alternatively, 1.5–1.875 mg GnRH-a was intramuscularly injected, lasting for 14–20 days until pituitary down-regulation was confirmed. Recombinant FSH and/or hMG were used in a similar manner as in the ultra-long protocol. If two or more follicles reached a maximum diameter of 19 mm, 250 μg of hCG (Ovidrel) was administered.

In the GnRH-a short-protocol, a dose of Leuprorelin (0.1 mg) was administered beginning on day 3 of the menstrual cycle. At the same time, ovarian stimulation commenced with 100–300 IU rFSH and/or hMG daily. The dosage of FSH and hMG was adjusted according to ovarian response. If two or more follicles reached a maximum diameter of 19 mm, 250 μg of hCG (Ovidrel) was administered.

GnRH-A protocol: 150–300 IU r-FSH and/or hMG was initiated on day 2 or 3 of the menstrual cycle until trigger day. GnRH-A (Cetrorelix; Merck Serono, France) at a dose of 0.25 mg was used daily until the trigger day, when the leading follicles reached a mean diameter of 14 mm. We stopped gonadotropin administration after observing that at least three follicles had reached a mean diameter of 18 mm and subsequently administered 250 μg of hCG.

Luteal phase support by vaginal administration of progesterone (600 mg/d) was initiated on day 1 after oocyte retrieval. Fresh embryo transplantation was carried out 48–72 h after oocyte retrieval. Fresh cycles were canceled if patients had an endometrial thickness <7 mm, if there was a high risk of ovarian

hyperstimulation syndrome (OHSS) (E2 ≥5000 pg/ml on the trigger day, and/or the number of oocytes obtained was ≥20) [21], no available embryos, or other personal reasons. Endometrial preparation for frozen-thawed embryo transfer (ET) consisted of an artificial cycle with 4 to 6 mg/day of oral estradiol. Progesterone (600 mg per day) was administered when the endometrium reached a depth of at least 8 mm.

Outcome measure

The outcomes that were evaluated included: the number of oocytes retrieved, the implantation rate, the miscarriage rate, the cumulative clinical pregnancy rate (cPR), and the cLBR. These outcome parameters were studied in the whole population. Patient characteristics were then compared between women who conceived and those who did not, looking for prognostic factors affecting ART outcome.

Pregnancy was diagnosed by a rising concentration of serum β-hCG, which was tested 14 days after ET. The implantation rate was defined as the number of gestational sacs observed divided by the number of embryos transferred [22]. Clinical pregnancies were determined by ultrasonographic documentation of at least one fetus with a heartbeat at 6–7 weeks of gestation [22]. Miscarriage was defined as pregnancy loss before 28 weeks. The cumulative cPR and cLBR were defined as the number of all eligible patients that underwent oocyte retrieval cycles within the study period who received a transfer and who had at least one clinical pregnancy and live birth, respectively, whether from the first transfer attempt or subsequent transfers of frozen–thawed supernumerary embryos [22].

Statistical analysis

Data were analyzed using software (SPSS, Version 23.0; IBM Corp, Armonk, NY, USA). The mean ± standard error of mean (SEM) was computed for every continuous variable. Categorical variables were expressed as proportions. Patient characteristics and ART outcome parameters were compared according to recurrence, using a Pearson x^2 test for qualitative variables, and Student *t*-test for quantitative variables. All statistical analyses were two-tailed, and $P<0.05$ was then considered to be significant. A binary logistic regression model was used to identify factors associated with cLBR. All factors associated with a $P < 0.15$ in univariate analysis were then tested in a multivariate model. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated from the model's coefficients.

Results

ART outcomes in patients with stage Ⅲ and Ⅳ ovarian endometriosis

Demographic data and clinical characteristics of the women with stage Ⅲ and Ⅳ endometriosis are summarized in Table 1. A total of 836 patients comprised of 734 women without and 102 with recurrent endometrioma during an ART cycle, representing 1048 IVF-ICSI cycles and 1160 embryo transfer cycles, were analyzed. The mean age of the population was 30.26 ± 0.11 y, 89 patients (10.65%) were 35–39 y old. The mean BMI was 21.35 ± 0.09 (kg/m^2). The mean duration of infertility was 3.32 ± 0.08 y, and

mean time interval between surgery and ART was 2.03 ± 0.07 y. Of the 836 women with stage Ⅲ and Ⅳ ovarian endometriosis, 290 patients (34.69%) had GnRH-a therapy after surgery, while 546 patients (65.31%) had no GnRH-a therapy. In all, 30 (3.59%) women had a history of surgery for endometrioma of more than twice. Moreover, 43 (5.14%) women in the study population had associated adenomyosis. The mean Ca125 level (U/ml) was 30.58 ± 1.45, the mean of day-3 FSH level (IU/L) was 7.17 ± 0.08, and mean AFC was 11.22 ± 0.15.

Out of all the 1048 cycles, 859 cycles achieved fertilization with IVF (81.97%); while in 189 cycles fertilization was achieved with ICSI (18.03%). In all the ET cycles, 708 (61.03%) were fresh ET cycles, and 452 (38.97%) were frozen-thawed ET cycles.

Overall, 549 (65.67%) women became pregnant and 507 (60.65%) had a live birth. Cumulative cPR per cycle and per ET cycle were 54.20% and 48.97%, respectively. cLBR per cycle and per ET cycle were 48.38% and 43.71%, respectively. There were 125 cycle cancelations (11.93%): 58 (46.4%) cycles were cancelled as there were no embryos for transfer, 15 (12.0%) for the absence of MII oocytes, 48 (38.4%) for fertilization failure or abnormal fertilization, and 4 (3.2%) for degradation of frozen-thawed embryos.

ART outcomes between women with primary and recurrent endometriomas

Clinical and biological characteristics of patients and cycles are summarized in Table 2. Female age, BMI, duration of infertility, early follicular phase serum FSH levels, day-3 estradiol levels, time of ovarian stimulation, total gonadotropin administration, and ART cycles were similar between the two study groups. As compared to women with primary endometriomas, time interval between surgery and ART was longer, and associated adenomyosis was higher in women with recurrent endometriomas ($P < 0.05$). In the recurrent group, the AFC, the estradiol level on hCG-day, and number of retrieved oocytes were significantly lower than those in the primary group ($P < 0.05$). In the COS protocols, ultra-long agonist was used more frequently in the recurrent group.

The fertilization rate, fresh/frozen-thawed embryos transferred cycles, cycle cancelation, implantation rate, and abortion rate were similar between the two groups. There were no significant differences between the recurrent group and primary group in the cumulative cPR per cycle (54.58% vs. 51.54%, $P = 0.515$) and per ET cycle (48.97% vs. 48.91%, $P = 0.988$). Furthermore, cLBR per cycle (48.69% vs. 46.15%, respectively, $P = 0.588$) and per ET cycle (43.70% vs. 43.80%, $P = 0.982$) were similar between the two study groups.

Prognostic factors of ART outcomes in patients with stage Ⅲ and Ⅳ endometriosis

As shown in Table 2, there were no significant differences in the cumulative cPR and LBR per cycle/ET cycle between the primary and recurrent groups, which may suggest that recurrence in patients <40 y with a normal ovarian reserve was not a poor prognostic factor for IVF-ICSI cLBR. Thus, further investigation is needed to determine which factors predict a poor prognosis for IVF-ICSI cLBR in women with stage III and IV endometriosis.

Univariate analysis comparing patients who delivered a live birth and those who did not is presented in Table 3. Age (OR 2.793; 95% CI, 1.776–4.392; P < 0.001), number of surgeries (OR 2.764; 95% CI, 1.298–5.886; P < 0.006), duration of infertility (OR 1.333; 95% CI, 1.007–1.765; P = 0.044), time interval between surgery and ART (OR 1.726; 95% CI, 1.301–2.289; P < 0.001), and associated adenomyosis (OR 2.234; 95% CI, 1.199–4.164; P = 0.01) were associated with lower cLBR. In addition, those patients with a lower AFC (OR 3.023; 95% CI, 2.232–4.094; P < 0.001) had a lower cLBR. Furthermore, this study showed that postoperative medication GnRH-a therapy did not influence cLBR.

As shown in Table 4, after multivariate analysis, we found an independent significant relationship with poor prognosis on cLBR for age ≥35 y (OR 0.362; 95% CI, 0.226–0.581; P < 0.001), time interval ≥2 y between surgery and ART (OR 1.482; 95% CI, 1.098–2.000; P = 0.01), and number of surgeries ≥2 (OR 0.406; 95% CI, 0.184–0.897; P = 0.026). Lower AFC was also associated with negative ART outcome (OR 2.741; 95% CI, 2.004–3.751; P < 0.001).

Discussion

In this observational study of 836 infertile patients (age <40 y) with stage Ⅲ–Ⅳ endometriosis undergoing ART, there was an overall pregnancy rate of 65.67% and 60.65% delivered a live birth. cLBR per cycle and per ET cycle reached 48.38% and 43.71% after four ART cycles, respectively. This study showed that ovarian responsiveness was significantly reduced in women with recurrent endometriomas undergoing an IVF/ICSI cycle after surgery. Indeed, the AFC, the estradiol level on hCG-day, and the number of oocytes retrieved were significantly lower, compared to the primary group. However, there were similar outcomes in the cumulative cPR/LBR between the two groups. Lastly, according to multivariate logistic regression analysis, an independent significant relationship with poor prognosis on cLBR in patients with stage Ⅲ and Ⅳ ovarian endometriosis for age (≥35), time interval between surgery and ART (≥2 years), number of surgeries (≥2), and AFC (<10) was found.

Surgical treatment of endometriosis could create a more favorable environment for successful conception [5]. On the other hand, surgical intervention for endometrioma may increase the risk of infertility by reducing the ovarian reserve [12, 13]. Previous reports on the impact of endometriosis severity on ART outcome have drawn conflicting conclusions. In previous studies, the IVF outcomes in patients with minimal/mild endometriosis were similar to those in patients for whom IVF was performed for other indications, while the outcomes were inferior in infertile patients with severe endometriosis. In cases with stage Ⅲ/Ⅳ endometriosis, fewer oocytes were retrieved, and lower implantation rates and cPR were reported [18, 19]. On the contrary, one study, which reviewed 3930 endometriosis cases, showed no difference in pregnancy outcome according to disease stage [23]. In the current study, cumulative cPR per cycle and per ET cycle reached 54.20% and 48.97% after four ART cycles. Maignien *et al* [24] recently conducted a retrospective observational cohort study showing that cumulative pregnancy rates reached 65.8% in a series of 359 endometriosis patients after four ART cycles. The higher cumulative PR than found in our study may be owing to an indistinctive description of disease stage. Other published studies show that the cumulative cPR can be from 38.6% to 43% in the rAFS stage Ⅲ and Ⅳ endometriosis patient,

although these sample sizes were relatively small [25, 26]. Such discrepancies could result from uncertainty about the exact endometriosis phenotype. An additional explanation may arise from exacerbating surgical approaches among patients with advanced pathology, which may impair ovarian reserve in cases of ovarian involvement.

Ovarian endometriosis is the most common type, and the recurrence rate following surgical intervention remains high. Since endometrioma is a pseudocyst, the risk of removing normal tissue during surgery is high. Therefore, there are concerns about reducing fertility and IVF outcome. Findings show that endometriomas, especially those that are recurrent endometriomas after surgical treatment, have a negative effect on the ovarian reserve [27, 28]. Likewise, in this study, it was observed that women with recurrent endometrioma after previous surgery for endometrioma had a lower AFC, estradiol level on hCG-day, and a lower number of total oocytes collected than the primary group. However, other studies record that cumulative cPR and LBR per started cycle in recurrent and primary endometrioma are similar [29, 30]. The current results also provided support for the conclusion that no significant differences were observed between recurrent and primary endometrioma in terms of cLBR and cPR in women with rAFS stage and endometriosis. The reasons possibly due to the young age (<40 y) in the recurrent group, and these patients have a relatively good ovarian reserve and small endometrioma cyst (<4 cm) in ART procedures. However, the current results found that advanced maternal age (≥35 y) had a higher risk of poor IVF outcome. This corresponded with results of retrospective-analyses [31]. The outcomes are likely based on the decline of both ovarian reserve and oocyte competence with advancing age. A study estimated that in women aged 35–37, 38–40, 41–42, and >42 y it was necessary to collect ∼5, 7, 10, and 20 oocytes, respectively, to identify at least one euploid embryo [32]. Therefore, women with severe endometriosis associated infertility should achieve pregnancy as soon as possible, and in patients >35 y who fail to get pregnant, IVF should be the treatment of choice.

Multivariate analysis indicated that a second surgery was a negative risk for cLBR. Clinicians are often faced with the decision of whether to undertake a second surgical procedure or to treat recurrent ovarian endometrioma with medical therapy. Current guidelines on the management of recurrent endometriosis suggests that clinicians should avoid repeated surgery in women who want to conceive when endometriosis has recurred after a first surgery [28]. However, the effect of secondary surgery on ART outcomes is still debated, with one study [33] reporting a similar PR after primary and secondary surgery while another study [27] reports poorer results after surgery for recurrence. In the present study, the lower cLBR was suggested to be linked with the second surgery. The reason for this result may be owing to the lower ovarian reserve in the recurrent endometrioma patients. The excised cyst wall in the specimens from patients with recurrent endometriomas were significantly thicker than in the specimens from patients undergoing surgery for the first time [12]. Furthermore, ovarian tissue was more abundant in the cyst wall of recurrent endometriomas than in the cyst wall after primary surgery [34]. As a result, AFC and ovarian volumes for the operated ovaries were significantly decreased in the recurrent endometrioma group. Therefore, if possible, clinicians should avoid a second surgery for recurrent endometriosis in women who plan to have further pregnancies. Clinicians may try postoperative medical treatment for recurrent endometriosis between IVF cycles.

In the current study, a statistically significant correlation was observed with the presence of adenomyosis, and this was associated with lower cLBR according to univariate analysis, but this did not remain a negative prognostic factor of IVF outcome after multivariate analysis. This agrees with some previous studies that show no impact of the disease on pregnancy rates [24, 35, 36]. Yet, data regarding the effect of adenomyosis on ART outcomes are still inconsistent. For instance, in a meta-analysis, Vercellini *et al* [37] show decreased clinical PR in patients with adenomyosis, as compared to controls. The negative results are probably owing to the presence of DIE, which is suggested to be a major negative predictive factor of ART results, decreasing cLBR from 51.9 to 19% [38]. The current study showed that the concurrent rate of adenomyosis was not a poor risk for cumulative LBR after excluding the factor of DIE. Therefore, correct identification of coexisting pathological conditions for DIE and adenomyosis is necessary for the development of effective IVF protocols.

GnRH-a is commonly administered for at least six months post-surgery to prevent the recurrence of endometriosis. In the current study, using the GnRH-a treatment after surgery was not associated with a poorer outcome of cLBR in infertile patients. These results are also supported by recent works, which indicate that postoperative ovarian suppression by GnRH-a is not helpful in enhancing PR [39]. In a recent prospective trial, women with mild endometriosis who received GnRH-a for three months before IVF improved their fertilization rate but not cPR [40]. The current data indicated that the GnRH-a ultra-long protocol was more frequently used in recurrent patients with severe endometriosis who achieved a similar cLBR as the primary group, which suggests that the GnRH-a ultra-long protocol can improve the cPR and cLBR of patients with recurrent endometrioma. These results may be explained by GnRH-a reducing inflammation, blood flow, and adhesions in endometriosis [41]. An additional explanation may arise from the lower levels of inflammatory cytokines that can reduce the toxic effects of cytokines on oocytes or embryos [42]. Despite these favorable results, some data show that long-term administration of GnRH-a could suppress the expression of implantation factors, which could lead to decreased endometrial receptivity [43]. In addition, long-term use of GnRH-a could induce side effects such as hot flashes, vaginal dryness, and decreased bone mineral density. Therefore, the potential benefits of GnRH-a pretreatment must be weighed against the ovarian reserve, additional costs, delays in the initiation of IVF, and the possibility of decreased response to ovarian stimulation.

Previous analyses demonstrate that there may be no effect of the interval from surgical management of endometriosis and IVF on PR throughout a 5-y evaluation period [44, 45]. However, an inverse result was observed in the current study; that is, the interval between surgical management of endometriosis and IVF had a significant effect on ART outcome for patients with advanced-stage endometriosis. We found that the cLBR was significantly higher when IVF was performed <2 y after surgery for endometriosis. Similarly, Nesbitt-Hawesetal *et al* [46] report a 13-month median time of surgery and IVF among patients with stage to endometriosis who conceived by ART. Other studies indicate that the highest ongoing PR can be achieved in patients undergoing their IVF cycle 6 to 25 months after their endometriosis surgery [47]. The reduced LBR after 2 y may be explained by either age factors, endometriosis recurrence, and/or ovarian reserve. Therefore, if IVF is planned after surgery for endometriosis, IVF delay may be considered to around 6 months but at no longer than 2 y.

The strength of this study was in the methodological design. First, the large number of patients with stage Ⅲ and Ⅳ ovarian endometriosis enrolled (836 women undergoing 1048 ART cycles), which will have increased the statistical power of the study. Second, although previous series exploring the relationship between endometriosis and ART exist in the literature, only a few focused on endometrioma. Third, only patients with a diagnosis of endometrioma based on histological confirmation after surgery were included. Nevertheless, the current study still had some limitations. The major limitation was its retrospective nature based on a single center, which may therefore contain bias regarding patient characteristics. Second, AMH was examined over 3 recent years in our hospital, therefore these results were not included in this study. The third limitation arose from the recurrent endometriomas being defined by ultrasound or MRI as the presence of a persistent ovarian cyst. This practice depended heavily on the skill and experience of radiologists. Moreover, the study population was represented by women <40 y, non-obese, with cleavage stage embryo transfer at day 2 or 3, so the data from this study can only be extrapolated to patients with a similar profile. Consequently, these limitations may have resulted in an under or over estimation of the associations in the results.

In conclusion, the current study suggests that postoperative recurrent endometriosis has no impact on ART outcome, whereas it did reduce the size of the ovarian reserve and the number of oocytes retrieved. Lower AFC (<10), age (≥35), number of surgeries (≥2), and time interval between IVF and surgery (≥2 y) were associated with a lower cLBR for women with rAFS III and IV endometriosis. These results might be useful in daily clinical practice to inform and counsel couples with rAFS Ⅲ and Ⅳ endometriosis before undertaking ART. No more than a 2-y interval between IVF and surgery should be recommended for these patients with advanced stage. These findings could also facilitate the identification of patients with poor chances of success with IVF-ICSI, thus avoiding unnecessary treatments and allowing the guidance of couples regarding alternative approaches. Further multi-center prospective studies are needed to confirm the results of this study and to support the management of infertile women with endometriosis.

Declarations

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Competing Interests

The authors declare that they have no conflict of interest.

Author Contributions

The study was designed by [Fang Le] and [Hangying Lou]. Material preparation, data collection and analysis were performed by [Quanmin Kang], [Xinyun Yang], [Yu Sun], [Ruizhe Chen] [Ning Wang] and [Huijuan Gao]. The first draft of the manuscript was written by [Fang Le]. The manuscript was edited by [Jin Fan] and [Yimin Zhu]. Hangying Lou and Yimin Zhu are co-corresponding authors. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

This study was approved by the Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine (IRB-20210319-R).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication of the tables in Table 1, 2, 3 and 4.

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Tables

Table 1. Patient characteristics and ART outcomes in women with rAFS stage and ovarian endometriosis (n = 836)

Characteristics	Values
Total population	836
Total cycles	1048
Age on the day of ART (mean ± SEM)	30.26± 0.11
35-39 years	89 (10.65%)
BMI, kg/m^2 (mean ± SEM)	21.35 ± 0.09
Parity	
0	763 (91.27%)
1	72 (8.61%)
2	1 (0.12%)
Gravidity	
0	565 (67.58%)
1	167 (19.98%)
2	62 (7.42%)
>=3	42 (5.02%)
Number of surgeries (>=2)	30 (3.59%)
Duration of infertility (mean ± SEM)	3.32 ± 0.08
< 3 years	379 (45.33%)
>=3 years	457 (54.67%)
Time between surgery and ART (mean ± SEM)	2.03 ± 0.07
GnRHa after surgery (3-6 months)	
Yes	290 (34.69%)
No	546 (65.31%)
rAFS endometriosis stages	
3	443 (52.99%)
4	393 (47.01%)
Associated male factor	76 (9.09%)
Associated tubal factor	317 (36.73%)
Associated adenomyosis	43 (5.14%)

Ca125 (U/mL)	30.58 ± 1.45
Previous surgery for endometrioma	
Unilateral	590 (80.57%)
Bilateral	246 (29.43%)
Ovarian reserve	
Day-3 FSH, IU/L	7.17 ± 0.08
Day-3 LH, IU/L	4.91 ± 0.07
Day-3 estradiol, pmol/L	126.47 ± 2.34
AFC	11.22 ± 0.15
Type of ART procedure	
IVF	859 (81.97%)
ICSI	189 (18.03%)
Presence of endometrioma during the cycle	102 (12.20%)
Controlled ovarian stimulation protocols	
ultra-long agonist	468 (44.66%)
Long agonist	269 (25.67%)
Antagonist	191 (18.22%)
Short agonist	120 (11.45%)
ART outcomes	**Values**
Time of COS (mean ± SEM, days)	10.74 ± 0.06
Total dose of gonadotropin (mean ± SEM)	2437.93 ± 3.91
Estradiol level on the hCG-day (pmol/L) (mean ± SEM)	10732.06 ± 231.04
Number of retrieved oocytes (mean ± SEM)	9.38 ± 0.16
Fertilization rate (mean ± SEM)	59.07 ± 0.82%%
Mean number of embryo transfer	1.78 ± 0.01
Cycles of fresh ET	708 (61.03%)
Cycles of frozen-thawed ET	452 (38.97%)
Cancellation rate	125/1048 (11.93%)

ART cycles（n = population）	
1	662 (79.19%)
2	143 (17.11%)
3	24 (2.87%)
4	7 (0.83%)
Pregnancies	549
Live births	507
Cumulative cPR per cycle	568/1048 (54.20%)
Cumulative cPR per ET cycle	568/1160 (48.97%)
Twin rate	120/549 (21.86%)
Implantation rate	686/2062 (33.27%)
Abortion rate	42/568 (7.39%)
Cumulative LBR per cycle	507/1048 (48.38%)
Cumulative LBR per ET cycle	507/1160 (43.71%)

Continuous data are presented as mean ± standard error of mean (SEM); categorical data are presented as no. (percentage).

ART, assisted reproductive technology; *y*: years; *BMI*, body mass index; *rAFS*, revised American Fertility Society; *IVF*, in vitro fertilization; *ICSI*, intracytoplasmic sperm injection; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *COS*, controlled ovarian stimulation; *AFC*, antral follicle count; *PR*, pregnancy rate; *ET*, embryo transfer; *LBR*, live birth rate.

Implantation rate: number of gestational sacs/number of embryos transferred.

Abortion rate: number of miscarriages/number of clinical pregnancies.

Table 2. Patient characteristics and comparison of ART outcome of primary vs. recurrent endometriomas

	Groups		P value
Characteristics	**Primary**	**Recurrence**	
Total population	734	102	
Total cycles	918	130	
Age on the day of ART (mean ± SEM)	30.34 ± 0.12	29.72 ± 0.34	0.071
BMI, kg/m2（mean ± SEM）	21.34 ± 0.10	21.40 ± 0.24	0.848
Previous pregnancy			0.404
No	672 (91.55%)	91 (89.22%)	
Yes	62 (8.45%)	11 (10.78%)	
Infertility			0.433
Primary	498 (67.85%)	67 (65.69%)	
Secondary	236 (32.15%)	35 (34.31%)	
Duration of infertility (mean ± SEM)	3.34 ± 0.08	3.14 ± 0.23	0.416
Time interval between surgery and ART	1.93 ± 0.07	2.73 ± 0.22	**0.001**
Associated male factor	68 (9.26%)	8 (7.84%)	0.640
Associated tubal factor	282 (38.42%)	35 (34.31%)	0.423
Associated adenomyosis	33 (4.50%)	10 (9.80%)	**0.023**
Number of surgeries（>=2)	25 (3.41%)	5 (4.90%)	0.586
GnRHa after surgery (3-6 months)	250 (34.06%)	40 (39.22%)	0.06
Ovarian reserve（mean ± SEM）			
Day-3 FSH, IU/L	7.16 ± 0.09	7.37 ± 0.22	0.402
Day-3 LH, IU/L	4.90 ± 0.08	5.08 ± 0.23	0.453
Day-3 estradiol, pmol/L	126.30 ± 2.54	130.21 ± 6.17	0.594
AFC	11.39 ± 0.16	10.00 ± 0.42	**0.002**
Type of ART procedure			0.184
IVF	747	112	

	(81.37%)	(86.15%)	
ICSI	171 (18.63%)	18 (13.85%)	
Controlled ovarian stimulation protocols			**0.001**
ultra-long agonist	390 (42.48%)	78 (60.00%)	
Long agonist	250 (27.23%)	19 (14.62%)	
Antagonist	170 (18.52%)	21 (16.15%)	
Short agonist	108 (11.77%)	12 (9.23%)	
ART outcomes	**Values**		
Time of COS (mean ± SEM, days)	10.75 ± 0.07	10.64 ± 0.18	0.509
Total dose of gonadotropin (mean ± SEM)	2423.44 ± 25.47	2537.93 ± 68.84	0.111
Estradiol level on the hCG-day (pmol/L) (mean ± SEM)	10968.96 ± 252.87	9055.07 ± 506.69	**0.010**
Number of retrieved oocytes (mean ± SEM)	9.54 ± 0.18	8.26 ± 0.43	**0.003**
Fertilization rate (mean ± SEM, %)	58.76 ± 0.88	61.29 ± 2.43	0.312
Embryo transfer cycles	1023	137	0.908
Cycles of fresh ET	625□61.09%□	83□60.58%□	
Cycles of frozen-thawed ET	398 (38.91%)	54 (39.42%)	
ART cycles□n = population□			0.297
1	585 (79.70%)	77 (75.49%)	
2	120 (16.35%)	23 (22.55%)	
3	23 (3.13%)	1 (0.98%)	
4	6 (0.82%)	1 (0.98%)	
Cycle cancelation	107/918 (11.66%□	18/130 (13.85%)	0.471
Pregnancies	484	65	

Live births	447	60	
Cumulative cPR per cycle	501/918 (54.58%)	67/130 (51.54%)	0.515
Cumulative cPR per ET cycle	501/1023 (48.97%)	67/137 (48.91%)	0.988
Implantation rate	606/1824 (33.22%)	80/238 (33.61%)	0.904
Abortion rate	37/501 (7.38%)	5/67 (7.46%)	0.989
Cumulative LBR per cycle	447/918 (48.69%)	60/130 (46.15%)	0.588
Cumulative LBR per ET cycle	447/1023 (43.70%)	60/137 (43.80%)	0.982

Continuous data are presented as mean ± standard error of mean (SEM); categorical data are presented as no. (percentage).

ART, assisted reproductive technology; *y*, years; *BMI*, body mass index; *IVF*, in vitro fertilization; *ICSI*, intracytoplasmic sperm injection; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *COS*, controlled ovarian stimulation; *AFC*, antral follicle count; *ET*, embryo transfer; *PR*, pregnancy rate; *LBR*, live birth rate.

A Pearson x^2 test for qualitative variables and Student *t*-test for quantitative variables between the two groups. Statistical significance was reached at $P < 0.05$.

Table 3. Prognostic factors of ART outcomes in women with rAFS stage and IV endometrioma

Characteristics	No live birth	≥ 1 live birth	OR (95% CI)	P value
Total population	329	507		
Total cycles	448	600		
Age (≥ 35 y)	55 (16.72%)	34 (6.71%)	2.793 (1.776-4.392)	**<0.001**
BMI, kg/m^2	21.50 ± 0.15	21.25 ± 0.11		0.918
Gravidity	0.54 ± 0.05	0.52 ± 0.04		0.922
Parity	0.09 ± 0.01	0.09 ± 0.01		0.617
Duration of infertility (≥ 3 y)	194 (58.97%)	263 (51.87%)	1.333 (1.007-1.765)	**0.044**
Recurrence of endometrioma	42 (12.77%)	60 (11.83%)	1.090（0.715-1.661）	0.688
Interval between surgery and ART (≥ 2 y)	161 (48.94%)	181 (35.70%)	1.726（1.301-2.289）	**<0.001**
Number of surgeries (≥ 2)	19 (5.78%)	11 (2.17%)	2.764（1.298-5.886）	**0.006**
GnRHa after surgery	116 (35.26%)	174 (34.32%)	1.042（0.779-1.394）	0.781
Ca125 (U/mL)	31.98 ± 2.50	29.64 ± 1.77		0.226
Associated male factor	32 (9.73%)	44 (8.68%)	1.134 (0.703-1.829)	0.607
Associated tubal factor	122 (37.08%)	195 (38.46%)	0.943 (0.708-1.256)	0.688
Ovarian reserve				
Day-3 FSH > 8, IU/L	46 (13.98%)	67 (13.21%)	1.067 (0.713-1.599)	0.751
Day-3 LH, IU/L	4.89 ± 0.12	4.95 ± 0.10		0.065
Day-3 estradiol, pmol/L	128.00 ± 3.86	125.54 ± 2.97		0.442
AFC < 10	149 (45.29%)	109 (21.50%)	3.023 (2.232-4.094)	**< 0.001**
Type of ART procedure			0.850 (0.619-1.166)	0.314
IVF	361 (80.58%)	498 (83.00%)		

ICSI	87 (19.42%)	102 (17.00%)		
Associated adenomyosis	25 (7.60%)	18 (3.55%)	2.234 (1.199-4.164)	**0.01**
Cycles of embryo transfer			0.927 (0.727-1.182)	0.54
Fresh ET cycles	263 (59.91%)	445 (61.72%)		
Frozen-thawed ET cycles	176 (40.09%)	276 (38.28%)		

Continuous data are presented as mean ± standard error of mean (SEM); categorical data are presented as no. (percentage).

ART, assisted reproductive technology; *y*, years; *BMI*, body mass index; *IVF*, in vitro fertilization; *ICSI*, intracytoplasmic sperm injection; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *COS*, controlled ovarian stimulation; *AFC*, antral follicle count; *OR*, odds ratios; *ET*, embryo transfer; *CI*, confidence intervals.

A Pearson x^2 test for qualitative variables and Student t-test for quantitative variables between the two groups. Statistical significance was reached at $P < 0.05$.

Table 4: Significant prognostic factors of ART after multivariate analysis

Characteristics	OR (95% CI)	P Value
Age ≥ 35 y	0.362 (0.226-0.581)	**<0.001**
Number of surgeries (≥ 2)	0.406 (0.184-0.897)	**0.026**
Duration of infertility (≥ 3 y)	1.211 (0.899-1.632)	0.208
Interval between surgery and ART (≥ 2 y)	1.482 (1.098-2.000)	**0.01**
AFC (<10)	2.741 (2.004-3.751)	**<0.001**
Associated adenomyosis	0.566 (0.293-1.093)	0.09

AFC, antral follicle count; *y*, years. *OR*, odds ratios; *CI*, confidence intervals.

Multivariate binary logistic regression analysis.