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PROGNOSTIC FACTORS FOR ASSISTED REPRODUCTIVE TECHNOLOGY IN WOMEN WITH ENDOMETRIOSIS RELATED INFERTILITY

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CONDENSATION:

While the type of endometriosis is not associated with assisted reproductive technology outcomes, previous history of surgery for any type of endometriosis is associate with decreased success.

SHORT VERSION OF TITLE:

ENDOMETRIOSIS AND ART OUTCOMES

ABSTRACT

Background: Assisted reproductive technology is one of the therapeutic options offered for managing endometriosis-associated infertility. Yet, published data on assisted reproductive technology outcome in women affected by endometriosis are conflicting and the determinant factors for pregnancy chances unclear.

Objective: To evaluate assisted reproductive technology outcomes in a series of 359 endometriosis patients, to identify prognostic factors and determine if there is an impact of the endometriosis phenotype.

Study Design: Retrospective observational cohort study, including 359 consecutive endometriosis patients undergoing in vitro fertilization or intra-cytoplasmic sperm injection, between June 2005 and February 2013 at a University Hospital. Endometriotic lesions were classified into 3 phenotypes - superficial peritoneal endometriosis, endometrioma, deep infiltrating endometriosis – based on imaging criteria (transvaginal ultrasound, magnetic resonance imaging); histological proof confirmed the diagnosis in women with a history of surgery for endometriosis. Main outcome measures were clinical pregnancy rates and live birth rates per cycle and per embryo transfer. Prognostic factors of assisted reproductive technology outcome were identified by comparing women who became pregnant and those who did not, using univariate and adjusted multiple logistic regression models.

Results: 359 endometriosis patients underwent 720 assisted reproductive technology cycles. One hundred and fifty-eight (44%) patients became pregnant, and 114 (31.8%) had a live birth. The clinical pregnancy rate and the live birth rate per embryo transfer was 36.4% and 22.8% respectively. The endometriosis phenotype (superficial endometriosis, endometrioma or deep infiltrating endometriosis) had assisted reproductive technology

outcomes. After multivariate analysis, previous history of surgery for endometriosis (OR (95% CI) = 0.14 (0.06-0.38)) or past surgery for endometrioma (OR (95% CI) = 0.39 (0.18-0.84)) were independent factors associated with lower pregnancy rates. AMH levels < 2ng/mL (OR (95% CI) = 0.51 (0.28-0.91)) and antral follicle count < 10 (OR (95% CI) = 0.27 (0.14-0.53)) were also associated with negative assisted reproductive technology outcomes.

Conclusion(s): The endometriosis phenotype seems to have no impact on assisted reproductive technology results. An altered ovarian reserve and a previous surgery for endometriosis and/or endometrioma are associated with decreased assisted reproductive technology outcomes.

KEYWORDS

Assisted reproductive technologies; endometriosis phenotypes; pregnancy; surgery; ovarian reserve

INTRODUCTION

Endometriosis (OSIS) is a benign chronic gynecological disease, defined as the presence of endometrial tissue outside the uterine cavity (1). Prevalence has been estimated to reach 10-15% of reproductive-aged women (2,3), and 25-50% of infertile women (4). It is widely accepted that endometriosis alters fertility, but the exact pathophysiology of this effect remains unclear. Current views suggest multifactorial mechanisms, including inflammatory changes in peritoneal fluid altering sperm-oocyte interaction, reduced functional ovarian tissue, and hampered endometrial receptivity (5).

Endometriosis is heterogeneous in nature with lesions having three distinct phenotypes: (i) superficial peritoneal endometriosis (SUP), (ii) ovarian endometrioma (OMA), and (iii) deeply infiltrating endometriosis (DIE) (6,7). Moreover, endometriosis is frequently associated with adenomyosis, which has detrimental effects on fertility of its own (8,9).

Assisted reproductive technologies (ART) are commonly offered for managing OSIS-related infertility. ART results however vary according to reports, with some showing identical outcome as in endometriosis-free counterparts (10–13), and others describing lower pregnancy rates (14–19). In this context of discordant ART results in endometriosis, there is no consensus about the possible impact of the OSIS phenotype on ART outcome. A recent meta-analysis from Rossi et al., comparing 980 OSIS patients to controls, pointed at decreased clinical pregnancy rates and live birth rates in stages III-IV endometriosis (19). Conversely, Barbosa et al. reviewing 3930 OSIS cases showed no difference in outcome according to disease stage (13). These discrepancies could result from important heterogeneity in the published series including: i) uncertainty about the exact endometriosis phenotype. Previous ART results published in endometriotic patients relied on the rAFS

classification (20) of the disease, which does not take into account the phenotype of lesions therefore, regrouping different forms of the disease under a same rAFS stage. Hence, precise phenotyping of lesions is needed for clarifying the impact of endometriosis on ART outcome; ii) confounding factors such as previous history of surgery for OMA and/or associated adenomyosis, which likely impacts on ART results, are rarely taken into account in retrospective studies (21).

To assess the impact of lesion phenotypes on ART outcome, we conducted an observational cohort study on a consecutive series of OSIS patients undergoing ART whose lesions had been prospectively phenotyped. The study objective was to analyze the possible role of endometriosis lesions phenotype (SUP/OMA/DIE) and to identify other potential prognostic factors of ART outcomes.

MATERIALS AND METHODS

Study Protocol

The local ethics committee (CCPPRB: Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of our institution approved the study protocol. The study population consisted of a continuous series of 359 phenotyped endometriosis patients who underwent IVF/ICSI treatment in a tertiary care center, between June 2005 and February 2013. Endometriotic lesions were classified according to their phenotype as superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA), or deeply infiltrating endometriosis (DIE) (6). All patients underwent an appropriate work-up (22) to precisely diagnose and stage endometriosis. For DIE and OMA phenotypes, diagnosis and staging of endometriosis was based on previously published imaging criteria using transvaginal

sonography (TVS) (23–25) or magnetic resonance imaging (MRI) (359 patients (100%) had TVS; 210 (58.5%) also had an MRI) (26–29). In addition, in women who had previous history of surgery for endometriosis, the diagnosis was also confirmed histologically. In SUP, pre-ART imaging work-up showing neither OMA nor DIE lesions, the diagnosis was solely based on previous histologically proved superficial peritoneal endometriotic lesion. These phenotypes being frequently combined, patients were assigned to the group corresponding to the most severe lesion, according to a previously published classification (30), going from the least to most severe: SUP, OMA, DIE.

All patients of OMA and DIE groups had superficial lesions. Women in the OMA group could not have DIE lesions, whereas some patients in the DIE group had associated OMA lesions. In case of DIE, the severity was assessed on the basis of two parameters (31): the number and anatomic location of DIE lesions. In cases of multiple DIE sites, patients were classified according to the worst finding (least to most severe: uterosacral ligament(s), vagina, bladder, intestine and ureter (32)). Associated adenomyosis was diagnosed using imaging criteria based on TVS and MRI (33).

General Characteristics

The study analysis used a prospectively managed database. For each patient, personal history data and results of fertility investigations were collected before ART treatment. The following data were recorded: age, height, weight, body mass index (BMI), parity, gravidity, duration of infertility, results of hysterosalpingography, cycle day 3 levels of follicle-stimulating hormone (FSH), luteinizing-hormone (LH), and estradiol (E2), anti-Müllerian hormone (AMH), antral follicle count (AFC) score and semen analysis as per World Health

Organization manual (34). For each patient, history of previous surgery for OSIS was recorded. Previous history of surgery was defined as excision of superficial lesions, deep lesions excision, bowel resection, or ovarian cystectomy. Women were then classified into two groups: previous surgery for OMA if they had a history of ovarian cystectomy with or without resection of SUP and/or DIE lesions, and previous surgery for OSIS without OMA if they had a history of surgery for OSIS (SUP and/or DIE) without associated ovarian cystectomy.

Controlled Ovarian Stimulation (COS) Regimen

Patients were stimulated either by a long gonadotropin-releasing hormone agonist (GnRH-a), a short agonist, or an antagonist protocol. In long GnRH-a protocol, ovarian stimulation was begun following pituitary desensitization with doses of gonadotropins ranging from 150 to 450 IU/day, depending on individual patient's characteristics. In case of antagonist protocol (n=167/720 cycles, 23.2%), GnRH antagonist was arbitrarily initiated on COS day 6. Both long and antagonist protocols were initiated following timely use of oral contraceptive (OC) pill (ethinyl E2: 0.03mg; levonorgestrel 0.125mg). In all cases, COS was initiated 6 days after discontinuing OC, using a mix of FSH and hMG preparation for palliating at the LH suppressing effects of OC (35). Oocyte pick-up was canceled in case of poor response, defined by the presence of less than 3 follicles measuring 17 mm or more, and/or estradiol levels under 750 pg/mL, at the time of the triggering decision. Transvaginal oocyte retrieval was scheduled 36 hours after human chorionic gonadotropin (hCG) administration and embryo transfer (ET) was performed 2 to 3 days later. The luteal phase was supported by vaginal administration of micronized progesterone (600 mg/day) from the day of oocyte

retrieval to the day of the first ultrasound at the fifth gestational week. Pregnancies were diagnosed by increasing concentrations of serum-hCG, 14 days after oocyte retrieval. ART results were assessed by analyzing the following outcomes: i) clinical pregnancies (36); ii) live births (36); iii) early miscarriages (37). These outcome parameters were studied in the whole population, and according to OSIS phenotypes. Patients' characteristics were then compared between women who conceived and those who did not, looking for prognostic factors affecting ART outcome.

Statistical Analysis

Data were analyzed using SPSS® version 12.0 (SPSS Inc. Headquarters, 233 S. Wacker Drive, 11th floor, Chicago, Illinois 60606, USA). Continuous data were presented as mean and standard deviations; categorical data, as number and percentages. Patients' characteristics and ART outcome parameters were compared according to OSIS phenotype, using a Pearson's X^2 test test for qualitative variables, and Kruskal-Wallis test for quantitative variables. If statistical significance was reached ($P < 0.05$), variables were compared two-by-two using Dunn's non-parametric comparison post-hoc test for quantitative variables, and Pearson's X^2 post test for qualitative variables; $P < 0.05$ was then considered to be significant. The Kaplan–Meier method was used to estimate the cumulative pregnancy rate (CPR).

When analyzing patients who became pregnant and those who did not, we used a Pearson's X^2 test for qualitative and Student's *t*-test for quantitative variables. Subsequently, the variables associated with pregnancy at the threshold of $P < 0.15$ in univariate analysis, were tested in a multiple logistic regression model taking into account several interactions

between variables. When two variables were highly correlated, we introduced in the model only one of them and suppressed the other, as for the number of DIE lesions ≥ 2 and intestinal DIE, the latter having been suppressed. After studying the interactions between all variables, we held back two significative interactions (previous surgery for OSIS without OMA and AFC; previous surgery for OMA and number of DIE lesions ≥ 2) and introduced the terms of these interactions in the model, as well as all variables selected as previously described. Odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated from the model's coefficients and their standard deviations. The final model was built using all selected significant variables in the multivariate analysis.

RESULTS

Study Population

Between June 2005 and February 2013, 359 phenotyped OSIS patients underwent 720 ART cycles at our tertiary care center. Demographic data and clinical characteristics of the study population are summarized in Table 1. The mean age of the population was 33.4 ± 4 years, and the mean duration of infertility was 4 ± 2.2 years (range: 1-12). Two hundred and seventy-seven (77.2%) patients suffered from primary infertility. Mean AMH level was 2.8 ± 2.2 ng/mL (range: 0.1-15), and mean AFC was 11 ± 6.7 (range: 2-56).

Endometriosis Phenotype

The OSIS phenotype was as follows: SUP, 49 patients (13.6%); OMA, 98 patients (27.3%); and DIE, 212 patients (59.1%). In 143 cases, DIE was associated with OMA lesions (67.5%).

The patients' distribution according to their worst DIE lesion was as follows: uterosacral ligament(s), 67 patients (31.6%); vagina, 10 patients (4.7%); bladder, 11 patients (5.2%); intestine, 118 patients (55.7%); and ureter, 6 patients (2.8%). The mean number of DIE nodules per patient was 2.1 ± 0.9 (range: 0-4).

Two hundred and eighty-two women (78.6%) had prior history of surgery for OSIS, with a mean number of previous surgeries of 1.3 ± 0.7 (range: 0-6). Of them, 170 (47.4%) had surgery for OMA. Complete exeresis of the lesions was achieved for 83 patients (23.1%). Moreover, 145 women of the study population (40.4%) had associated adenomyosis.

ART Outcomes

In total, 720 ART cycles associated with 500 embryo transfers were analyzed. ART outcome in the general population are shown in Table 1. Overall, 158 women (44%) became pregnant and 114 (31.8%) had a live birth. Clinical pregnancy rate (cPR) and live birth rate (LBR) per ET were 36.4% and 22.8%, respectively. Cumulative pregnancy rate (CPR) was 18.2% after one ICSI-IVF cycle, 36.4% after two ICSI-IVF cycles, 50.2% after three ICSI-IVF cycles and 65.8% after four ICSI-IVF cycles. Cancellation rate was 30.6%: 190 (86.4%) cycles were cancelled for poor response, 20 (9.1%) for absence of oocyte or fertilization failure, and 10 (4.5%) for poor embryo quality.

Patients' characteristics and IVF results according to the OSIS phenotype are presented in Table 2. All patients in the SUP group had a history of previous surgery, compared to the OMA (80.6%) and DIE (72.6%) groups ($p<0.001$). DIE patients had a significantly lower AFC (11 ± 6.4) than SUP patients (14 ± 8) ($p=0.013$). The prevalence of associated adenomyosis was higher in the DIE group (56.6%), than in the SUP (14.3%) and OMA (18.4%) groups

(p<0.001). Clinical pregnancy rates and live birth rates did not differ between the three groups. Cancellation rate was higher in DIE patients (33.6%), compared to SUP (18.9%) and OMA (29.5%) patients (p=0.018). Miscarriage rate was higher in the SUP group (55.2%), than in the OMA (40%) and DIE (30.6%) groups (p=0.049).

Prognostics Factors of ART outcomes

Univariate analysis comparing patients who became pregnant and those who did not is presented in Table 3. Multifocality of DIE lesions (OR (95% CI) = 0.33 (0.18-0.59)), DIE with intestinal involvement (OR (95% CI) = 0.38 (0.24-0.60)), and associated adenomyosis (OR (95% CI) = 0.63 (0.41-0.97)) were associated with significantly lower fertility results. History of previous surgery for OSIS (OR (95% CI) = 0.50 (0.28-0.90)) or OMA (OR (95% CI) = 0.37 (0.21-0.64)) was associated with lower pregnancy rates. Those patients also had worst ovarian reserve parameters, with a higher proportion of day 3 FSH > 8 IU/L (OR (95% CI) = 0.51 (0.32-0.81)), AMH serum levels < 2 ng/mL (OR (95% CI) = 0.35 (0.22-0.55)), and AFC < 10 (OR (95% CI) = 0.31 (0.20-0.50)).

After multivariate analysis, past surgery for OSIS (OR (95% CI) = 0.14 (0.06-0.38)) or OMA (OR (95% CI) = 0.39 (0.18-0.84)), AMH levels < 2 ng/mL (OR (95% CI) = 0.51 (0.28-0.91)) and AFC < 10 (OR (95% CI) = 0.27 (0.14-0.53)) remained independent factors associated with lower pregnancy rates, as displayed in Table 4.

COMMENT

Main Findings

In this observational cohort study of 359 infertile OSIS patients undergoing ART, 44% ultimately achieved pregnancy, and 32% had a live birth. cPR and LBR per ET were 36.4% and 22.8%, respectively. Using the Kaplan-Meier method, cumulative pregnancy rates reached 65.8% after four ART cycles. The OSIS phenotype seemed to have no impact on ART outcomes, whereas history of previous surgery for OSIS/OMA and diminished ovarian reserve (AMH < 2 ng/mL, AFC < 10) were associated with lower pregnancy rates, after multivariate analysis.

Strengths and Limitations

The strength of this study lies in the methodological design: i) the large number of endometriotic patients enrolled (359 women undergoing 720 ART cycles), and the large number of severe forms of the disease (212 DIE patients, with 55.7% of intestinal lesions), may have Increased the statistical power of the study; ii) although previous series exploring the relationship between endometriosis and ART exist in the literature, none focused on endometriosis phenotypes (SUP, OMA or DIE). Given the considerable disease heterogeneity, the present study benefits from sorting ART outcome according to well-defined phenotypes (SUP, OMA or DIE). This anatomical classification describes the disease phenotype more relevantly than the rAFS classification (20): Indeed, rAFS may include different type of endometriotic lesions in the same stage; iii) our study, only included patients whose diagnosis of endometriosis was based on stringent surgical and/or imaging criteria; iv) finally, numerous epidemiological variables were prospectively collected using questionnaires before ART (concerning surgical history, infertility data and ovarian stimulation characteristics), which may constitute potential confounding factors.

It remains however that our study suffers from certain limitations and/or biases. In 21.4% of patients there was no previous history of surgery and therefore no surgical/histological proof of endometriosis. However for all study participants, endometriosis was diagnosed and staged using imaging techniques to assess for OMA and DIE phenotypes. This limitation – lack of surgical/histological confirmation of diagnosis – is one that affects most studies on OSIS and ART and is therefore not entirely avoidable. Moreover, owing to the retrospective design of the study, specific details regarding the type of previous surgery for endometriotic lesions were not available, so that we could only distinguish surgeries with or without ovarian cystectomy for OMA. However, considering the high rate of DIE lesions at the time of IVF among patients with a history of surgery (55%), we believe that many surgeries were incomplete, therefore minimizing the impact of this lack of information. In addition, this study was conducted in a referral center that specialises in endometriosis surgery. Therefore, women referred to our center may have suffered from particularly severe forms of endometriosis, especially those with a history of surgery, which introduces potential selection and comparison bias. Indeed, those women are likely to be the most severe cases as previously shown in the literature (38), and therefore may have the worst fertility prognosis. Yet, the proportion of DIE patients was higher in the group with no history of surgery than in the group with previous surgery (75% versus 55%, $p = 0.001$), tempering the idea that the most severe cases of endometriosis were in the “previous surgery” group, and thus, limiting the comparison bias. The analysis of IVF outcomes by pooling results of different ovarian stimulation protocols could also be seen as a limitation of our study. Yet, GnRH-agonist or antagonist protocols seem to be equally effective in endometriotic patients (39,40). Finally, we cannot exclude the existence of potential associated other causes of infertility in our group of infertile endometriosis affected women.

Interpretation

Our results, showing similar pregnancy rates and live birth rates in the three OSIS phenotypes bring a new insight in this complex disorder, considering that all publications in literature are exclusively based on rAFS classification (20). Previous reports on the impact of OSIS severity on ART outcome drew conflicting conclusions. For example, in a recent meta-analysis from Barbosa et al. including 2227 stage I/II OSIS patients and 1703 stage III/IV patients, no significant difference was found concerning clinical pregnancy rates (38% vs 34.2%, RR= 0.90, 95% CI 0.82-1.00) or live birth rates (28.2% vs 26.5%, RR = 0.94, 95% CI 0.80-1.11) (13). On the contrary, in another meta-analysis involving 6914 women, Rossi et al. showed lower pregnancy rates in stage III/IV patients compared to controls (OR = 0.45, 95% CI 0.29-0.70)(19). Interpreting these discrepancies is complex, due to great heterogeneity in study populations: i) the rAFS classification (20) often musters several phenotypes in a same stage; ii) most studies retrospective in nature lack of information about previous surgeries, which can bring confounding factors; iii) associated-adenomyosis is rarely diagnosed and taken into account. Analyzing ART outcomes according the anatomical classification of OSIS lesions might help guiding clinical decisions in daily practice. The fact that the OSIS phenotype is not correlated to IVF/ICSI results should indeed be considered when choosing the best treatment between ART and surgery, in women desiring to conceive (6).

In addition, we found that a history of previous surgery for OSIS or OMA is associated with poor IVF outcomes, as Rossi et al. suggested in a recent meta-analysis (19). The known impact of surgery for OMA on ovarian reserve could explain these results. For instance, Streuli et al. demonstrated that AMH levels were significantly decreased in endometriosis

women who had prior OMA surgery, compared to women who never underwent surgery (OR = 3.0, 95% CI 1.4-6.41, p = 0.01) (41). In another study, Somigliana et al. showed significantly impaired IVF outcomes in patients previously operated for bilateral OMA (42). Finally, an intriguing finding was reported by Roustan et al. who described lower LBR in women with diminished ovarian reserve diagnosed after OMA surgery as compared to idiopathic diminished ovarian reserve (43). Likewise, we observed in this study that women with previous surgery for OSIS without associated ovarian surgery still had lower pregnancy rates. Even if we don't have precise informations about the type of surgery in this group of patients, it suggests that the impact of pelvic surgery is not only linked to direct ovarian damage, but might also involve other mechanisms. Besides, two recent Chinese studies highlighted that surgery activates adrenergic signaling and increases angiogenesis thereby, promoting growth of endometriotic lesions (44,45). In striking contrast, some authors suggest that a complete removal of endometriosis lesions by skilled surgeons improves IVF outcomes (46). Some studies even show that extensive laparoscopic surgery enhances fertility outcomes in endometriosis patients with repeated IVF implantation failures (47). Yet, in such studies we might wonder whether increased pregnancy rates are linked to the surgical procedure or to the repetition of IVF cycles, since the cumulative live birth rate continues to increase up to the sixth cycle (48). Such controversial results underline the need for randomized clinical trials to assess the role of surgery in endometriosis-related infertility and urge us to carefully weight the pros and cons before offering surgery to OSIS patients suffering from infertility. A global and multidisciplinary approach is needed, and fertility preservation strategies might be considered for some women, before surgery (6).

Another notable finding was that adenomyosis was associated with lower pregnancy rates in univariate analysis, but did not remain a negative prognostic factor of IVF outcome

after multivariate analysis. This is in agreement with several previous studies, which showed no impact of the disease on pregnancy rates (49–54). Yet, the effect of adenomyosis on ART outcomes is still debated. For instance, Ballester et al. found that adenomyosis – present in 75 patients with intestinal DIE – was a major negative predictive factor of ART results, decreasing cumulative LBR from 51.9% to 19% (55). In a recent meta-analysis, Vercellini et al. confirmed this view, showing decreased clinical pregnancy rates (40.5%) in 304 patients with adenomyosis, as compared to controls (49.8%) (21). In our study population, the high prevalence of DIE – strongly associated with adenomyosis (8,9) – may limit our ability of assessing the impact of adenomyosis *per se* on ART outcome. Further large prospective cohort studies, with harmonized diagnostic modalities and adjustment on potential confounding factors (associated OSIS, ovarian reserve, embryo quality) are required in order to draw solid conclusions.

Overall, our study suggests that the OSIS phenotype has no impact on ART outcome, whereas, diminished ovarian reserve (AFC < 10, AMH < 2 ng/mL) and past surgery for OSIS/OMA are associated with lower outcomes. These findings might be useful in daily clinical practice for offering an optimal management of infertile OSIS women and help them choose between reverting to ART or surgery. Yet, further prospective studies taking into account the type of surgery are needed to draw firm conclusions.

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TABLES

Table 1

Patients' characteristics and ART outcomes in the general population (n = 359).

Characteristics[a]	Values
Age (years)	33.4 ± 4.0
Body Mass Index (kg/m^2)	22.5 ± 3.5
Duration of prior infertility (years)	4.0 ± 2.2
Gravidity:	
0	262 (73%)
1	69 (19.2%)
2	17 (4.7%)
≥ 3	11 (3.1%)
Parity:	
0	318 (88.6%)
1	35 (9.7%)
≥ 2	6 (1.7%)
Type of infertility:	
Primary	277 (77.2%)
Secondary	82 (22.8%)
Associated male factor	67 (18.7%)
Associated tubal factor	38 (10.6%)
Endometriosis phenotype	
SUP	49 (13.6%)
OMA	98 (27.3%)

DIE	212 (59.1%)
Without associated OMA lesions	69 (32.5%)
With associated OMA lesions	143 (67.5%)
Previous surgery for OSIS	282 (78.6%)
Number of prior surgeries	1.3 ± 0.7
Previous surgery for OMA	170 (47.4%)
Number of prior surgeries	1.2 ± 0.6
Right	47 (27.7%)
Left	66 (38.8%)
Bilateral	57 (33.5%)
Complete surgical exeresis of endometriotic lesions	83 (23.1%)
Ovarian reserve:	
Day 3 FSH (IU/L)	7.7 ± 4.2
Day 3 LH (IU/L)	5.3 ± 2.8
Day 3 Estradiol (pg/ml)	45.0 ± 26.3
AFC	11.0 ± 6.7
AMH (ng/ml)	2.8 ± 2.2

ART Outcomes	Numerator/Denominator, (%)
ART cycles	720
Cycle 1	359
Cycle 2	220
Cycle 3	103
Cycle 4	38

Embryo transfers	500
Cancellation rate	220/720 (30.6%)
Pregnancies	158 (44%)
Live births	114 (31.8%)
Clinical pregnancy rate per cycle	182/720 (25.3%)
Clinical pregnancy rate per embryo transfer	182/500 (36.4%)
Implantation rate [b]	208/918 (22.7%)
Abortion rate [c]	68/182 (37.4%)
Live birth rate per cycle	114/720 (15.8%)
Live birth rate per embryo transfer	114/500 (22.8%)

Note: ART = assisted-reproductive technologies; OSIS = endometriosis; SUP = superficial endometriosis; OMA = endometrioma; DIE = deep infiltrating endometriosis; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AFC = antral follicle count; AMH = anti-Müllerian hormone

[a] *Continuous data are presented as mean ± standard deviation; categorical data are presented as number (percentage)*

[b] *Implantation rate = number of gestational sacs / number of embryos transferred*

[c] *Abortion rate = number of miscarriages / number of clinical pregnancies*

566 **Table 2**
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568 **Patients' characteristics and ART outcomes according to the endometriosis**
569 **phenotype.**
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Characteristics [a]	**OSIS Phenotypes**			**P-value**
	SUP	**OMA**	**DIE**	
	(n = 49)	(n = 98)	(n = 212)	
Age (years)	33.9 ± 3.6	34.1 ± 4.1	33.0 ± 4.0	0.092 [w]
BMI (kg/m2)	22.6 ± 3.7	22.0 ± 3.4	22.8 ± 3.6	0.178 [w]
Gravidity	0.5 ± 1.0	0.4 ± 0.7	0.4 ± 0.8	0.829 [w]
Parity	0.1 ± 0.3	0.1 ± 0.4	0.1 ± 0.4	0.741 [w]
Duration of prior infertility (years)	4.0 ± 2.0	4.0 ± 2.4	4.0 ± 2.1	0.181 [w]
Type of infertility				0.856 [k]
Primary	37 (75.5%)	77 (78.6%)	163 (76.9%)	
Secondary	12 (24.5%)	21 (21.4%)	49 (23.1%)	
Associated male factor	9 (18.4%)	25 (25.5%)	33 (15.6%)	0.113 [k]
Associated tubal factor	5 (10.2%)	6 (6.1%)	27 (12.7%)	0.212 [k]
Previous surgery for endometriosis	49 (100%)[b]	79 (80.6%)	154 (72.6%)	< 0.001 [k]
Ovarian reserve				
Day 3 FSH (IU/L)	8.3 ± 5.4	7.8 ± 2.9	7.5 ± 4.4	0.196 [w]
Day 3 LH (IU/L)	4.9 ± 2.1	5.7 ± 2.7	5.2 ± 2.9	0.125 [w]
Day 3 Estradiol (pg/ml)	45.0 ± 19	43.0 ± 22.7	45.0 ± 29.3	0.696 [w]
AFC	14.0 ± 8.0	12.0 ± 6.2	11.0 ± 6.4 [c]	0.013 [w]
AMH (ng/ml)	2.8 ± 1.8	3.1 ± 2.6	2.6 ± 2.1	0.398 [w]
Associated adenomyosis	7 (14.3%)	18 (18.4%)	120 (56.6%)[d]	< 0.001 [k]

ART Outcomes	Numerator/Denominator, (%)			
ART cycles	95	200	425	
Cancellation rate	18/95 (18.9%)	59/200 (29.5%)	143/425[g] (33.6%)	0.018 [k]
Clinical pregnancy rate per cycle	29/95 (30.5%)	55/200 (27.5%)	98/425 (23.1%)	0.22 [k]
Clinical pregnancy rate per ET	29/77 (37.7%)	55/141 (39%)	98/282 (34.8%)	0.67 [k]
Implantation rate [e]	35/140 (25%)	62/265 (23.4%)	111/513 (21.6%)	0.66 [k]
Abortion rate [f]	16/29[h] (55.2%)	22/55 (40%)	30/98 (30.6%)	0.049 [k]
Live birth rate per cycle	13/95 (13.7%)	33/200 (16.5%)	68/425 (16%)	0.82 [k]
Live birth rate per ET	13/77 (16.9%)	33/141 (23.4%)	68/282 (24.1%)	0.40 [k]

Note: ART = assisted-reproductive technologies; SUP = superficial endometriosis; OMA = endometrioma; DIE = deep infiltrating endometriosis; BMI = body mass index; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AFC = antral follicle count; AMH = anti-Müllerian hormone; ET = embryo transfer

[a] Continuous data are presented as mean ± standard deviation ; categorical data are presented as number (percentage)

[w] Kruskal-Wallis test

[k] Pearson's Chi-square test

[b] Statistically different from OMA (p<0.001) and DIE (p<0.001) after Pearson's Chi-square post test

[c] Statistically different from SUP (p<0.05) after Dunn's non-parametric comparison post-hoc test

[d] Statistically different from SUP (p<0.001) and OMA (p<0.001) after Pearson's Chi-square post test

583 [e] *Implantation rate = number of gestational sacs / number of embryos transferred*

584 [f] *Abortion rate = number of miscarriages / number of clinical pregnancies*

585 [g] *Statistically different from SUP (p=0.005) after Pearson's Chi-square post test*

586 [h] *Statistically different from DIE (p=0.016) after Pearson's Chi-square post test*

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591 **Table 3**

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593 **Prognostic factors of ART outcomes. Results from the univariate analysis.**

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Characteristics [a]	**Pregnancy –** (n=201)	**Pregnancy +** (n=158)	**OR (95% CI)**	**P-value**
Age > 35 years	90 (44.8%)	54 (34.2%)	0.64 (0.42-0.99)	0.042 [k]
BMI (kg/m^2)	22.8 ± 3.7	22.2 ± 3.4		0.174 [t]
Gravidity	0.4 ± 0.9	0.3 ± 0.7		0.247 [t]
Parity	0.1 ± 0.4	0.1 ± 0.4		0.608 [t]
Type of infertility			1.18 (0.72-1.04)	0.462 [k]
Primary	158 (78.6%)	119 (75.3%)		
Secondary	43 (21.4%)	39 (24.7%)		
Associated male factor	37 (18.4%)	30 (19%)	1.04 (0.61-1.77)	0.888 [k]
Associated tubal factor	20 (10%)	18 (11.4%)	1.16 (0.59-2.28)	0.663 [k]
Duration of prior infertility (years)	4.1 ± 2.1	4.0 ± 2.3		0.663 [t]
Endometriosis phenotype				0.065 [k]
SUP	22 (10.9%)	27 (17.1%)	10.78 (0.39-	
OMA	50 (24.9%)	48 (30.4%)	1.56)	
DIE	129 (64.2%)	83 (52.5%)	0.52 (0.28-1.00)	
Number of DIE lesions ≥ 2	83 (41.3%)	36 (22.8%)	0.33 (0.18-0.59)	< 0.001 [k]
Intestinal DIE	85 (42.3%)	33 (20.9%)	0.38 (0.24-0.60)	< 0.001 [k]
History of surgery for OSIS/OMA				0.002 [k]
No surgery	30 (15%)	47 (31%)	1	
Surgery for OSIS without OMA	63 (31.3%)	49 (31%)	0.50 (0.28-0.90)[b]	
Surgery for OMA	108 (53.7%)	62 (39.2%)	0.37 (0.21-0.64)[c]	

Ovarian reserve				
Day 3 FSH > 8 (IU/L)	74 (36.8%)	38 (24.1%)	0.51 (0.32-0.81)	0.010 [k]
Day 3 LH (IU/L)	5.3 ± 3	5.3 ± 2.4		0.834 [t]
Day 3 Estradiol (pg/ml)	45.9 ± 27.7	42.9 ± 24.4		0.301 [t]
AMH < 2 (ng/ml)	103 (51.2%)	42 (26.6%)	0.35 (0.22-0.55)	< 0.001 [k]
AFC < 10	101 (50.2%)	43 (27.2%)	0.31 (0.20-0.50)	< 0.001 [k]
Number of ART cycles ≥ 3	52 (25.9%)	51 (32.3%)	1.37 (0.86-2.16)	0.182 [k]
Associated adenomyosis	91 (45.3%)	54 (34.2%)	0.63 (0.41-0.97)	0.034 [k]

Note: ART = assisted-reproductive technologies; OR = odds ratio; CI = confidence interval; BMI = body mass index; DIE = deep infiltrating endometriosis; OMA = endometrioma; SUP = superficial endometriosis; OSIS = endometriosis; FSH = follicle-stimulating hormone; LH = luteinizing hormone; AMH = anti-Müllerian hormone; AFC = antral follicle count

[a] *Continuous data are presented as mean ± standard deviation ; categorical data are presented as number (percentage)*

[b] *Statistically different from No surgery (p=0.019) after Pearson's Chi-square post test*

[c] *Statistically different from No surgery (p<0.001) after Pearson's Chi-square post test*

[k] *Pearson's Chi-square test*

[t] *Student's t test*

Table 4

Significant prognostic factors of ART outcomes after multivariate analysis.

Characteristics	OR (CI 95%) [a]	P-value
AMH < 2 ng/ml	0.51 (0.28-0.91)	0.024
AFC < 10	0.27 (0.14-0.53) [b]	< 0.001
Previous surgery for OSIS without OMA	0.14 (0.06-0.38)	< 0.001
Previous surgery for OMA	0.39 (0.18-0.84)	0.016

Note: ART = assisted-reproductive technologies; AMH = anti-Müllerian hormone; AFC = antral follicle count ; OSIS = endometriosis; OMA = endometrioma

[a] *Odds Ratio (95% Confidence Interval)*

[b] *Odds Ratio for no previous surgery for OSIS and OMA*