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Non-ART pregnancy predictive factors in infertile patients with peritoneal superficial endometriosis

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ABSTRACT

Objective: To study the predictive factors for non-ART pregnancy in infertile women after laparoscopic diagnosis and surgery for isolated superficial peritoneal endometriosis (SUP).
Study design: Retrospective observational study from January-2004 to December-2015 in a tertiary care university hospital and Assisted Reproductive Technology (ART) centre. Infertile women with laparoscopic surgery for SUP (with histologic diagnosis) were included. The surgical treatment was followed by spontaneous fertility or post-operative ovarian stimulation (pOS) using superovulation (gonadotrophins) ± Intra Uterine Insemination (IUI). The main outcomes were the non-ART clinical pregnancy rates and its predictive factors.
Result(s): Over the period study, 315 women were included. Of these, 133 (42.3%) women had non-ART pregnancy. The mean time to conceive was 6 months (±6 days). Univariate analysis for non-ART pregnancy after surgery showed that: (i) no difference was observed according to age, length of infertility, Body Mass Index (BMI), the rate of previous pregnancy, and the pre-operative ovarian stimulation rate; (ii) diminished ovarian reserve and previous miscarriage were higher in the non-pregnant women group (8.3 versus 19.1%, $p < 0.05$; 3.5% versus 9%, $p = 0.06$, respectively); (iii) the mean EFI score and pOS were higher in pregnant women (7.7 versus 7.2, $p = 0.02$; 49.2% versus 26.7%, $p < 0.01$); and (iv) IUI did not show any benefit for pregnancy (22% after superovulation versus 27.2% after superovulation and IUI). In the multivariate analysis, only pOS (adjusted OR 2.504, 95% CI [1.537–4.077]) and DOR (aOR 0.420, 95% CI [0.198–0.891]) remained significantly associated with the incidence of pregnancy.
Conclusion(s): After laparoscopic surgery for peritoneal superficial endometriosis related infertility, ovarian stimulation improved pregnancy rate, while diminished ovarian reserve had a worse prognosis for pregnancy.

Introduction

European and American actual guidelines [1,2] for endometriosis related to infertility management mostly involved the disease stages using the American Society Reproductive Medicine classification (ASRM) or the revised American Society Fertility score (rAFS) [3,4], and proposed several different practices for minimal to mild (Stage I–II) and moderate to severe endometriosis (Stage III–IV). However, these classifications have never demonstrated their usefulness for post-operative fertility management [5,6]. Indeed, 3 different forms of endometriosis (peritoneal superficial endometriosis, endometrioma, deep infiltrating endometriosis – DIE – with or without bowel involvement) emerged with specific data. These 3 endometriotic phenotypes can be associated and could lead to confounding factors in the infertile endometriotic patients' population. Moreover, tubal adnexal evaluation, previous complete or incomplete surgery, associated adenomyosis, and ovarian reserve have been shown to be other confounding factors limiting the relevance of available data. So, the link between the lesion types and infertility was far from clear.

Recently, Endometriosis Fertility Index has shown its interest for post-operative spontaneous pregnancies in endometriosis related infertility management [7–9].

Peritoneal superficial endometriosis (SUP) seemed to be the more common lesion [10,11] in infertile patients with

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endometriosis laparoscopic diagnosis. However, its relationship and impact on fecundability, has been questioned by some authors [12,13] while others found that SUP was clearly associated with infertility [14–17]. The heterogeneity of the studied population and the use of ASRM staging do not provide any valuable contribution to assess the post-operative fertility. Hence, for isolated SUP in infertile patients, post-operative management, and predictive factors for non-IVF pregnancy remained unclear. The aim of our study was to assess predictive factors for non-IVF pregnancy in patients with SUP related infertility.

Patients and methods

Study design and patient selection

We conducted a retrospective observational study of all consecutive infertile patients treated for infertility, who underwent a laparoscopy with histologic diagnosis and treatment of superficial peritoneal endometriosis and who were offered a non-IVF conception for at least 6 months from January, 1st 2004 to December, 31st 2015.

Data were gathered from a tertiary care university hospital registry. The study was approved by the Institutional Review Board that allowed retrospective and prospective studies. All women underwent surgery in our University Hospital, and were informed that data were routinely and prospectively entered into an electronic record keeping system for contributing to the PMSI (national "Programme de médicalisation des systèmes d'information") database, and that indicators were analyzed. Therefore, informed consent was obtained from each subject before beginning surgery. Then, these data were reviewed by a professional data management.

After a 12 months infertility period, the study population met the following criteria: (i) asymptomatic or pelvic pain (dysmenorrhea, and/or deep dyspareunia), (ii) normal or abnormal clinical examination, (iii) normal or abnormal hysterosalpingogram, (iv) normo-ovulation or failure to conceive after 3 cycles of superovulation with or without intra-uterine insemination (IUI), (v) laparoscopic superficial peritoneal endometriosis diagnosis; and (vi) normal partners' semen analyses according to the WHO criteria, respectively [18].

Indications for laparoscopy were (possibly more than one per patient): pelvic pain (dysmenorrhea, and/or deep dyspareunia), abnormal hysterosalpingogram, failure to conceive after 3 or more cycles of superovulation with or without intra-uterine insemination (IUI).

Women with endometrioma, DIE, myoma, and/or focal or diffuse adenomyosis were excluded after clinical, pelvic ultrasound scan, MRI, and surgical observations.

Surgical procedure

Complete surgical treatment of all recognizable endometriotic lesions was performed whenever possible. Asymptomatic peritoneal endometriotic lesions were also treated. Surgical treatment of SUP was performed by electrocoagulation, plasma ablation, or excision. Complete pelvic adhesiolysis was performed. Transient abdominal ovariopexy was performed using a non-adsorbable thread for patients who had undergone complete adhesiolysis and endometriotic lesion removal with a revised American Fertility Score (rAFS), above 8 per adnexa [19]. Adhesion recurrence prevention was performed for patients with rAFS score above 6 or in cases with large peritoneal excision by hydro-flotation with icodextrin (Adept [4% icodextrin]; Baxter, Maurepas, France) or by hyaluronic acid gel application (Hyalobarrier; Nordic Pharma France, Paris, France).

EFI was calculated retrospectively for all patients. Evaluation of the least function score was retrospectively performed with a double-blinded calculation, performed by the operative surgeon and another surgeon specialized in endometriosis and infertility using operative reports [8]. Discrepancy between the two surgeons (JB, CP) was less than 1% (data not shown).

Post-operative management

Postoperative care, and the choice to perform a superovulation with or without intrauterine insemination were decided during a multidisciplinary meeting. No hormonal suppression was prescribed since all patients desired to become pregnant. When superovulation was decided, stimulated cycles were performed using recombinant or urinary gonadotrophins (Follitropin alpha GonalF®, Merck-Serono, Lyon, France; Follitropin beta Puregon®, MSD, Neuilly, France) in order to achieve 2 or 3 mature follicles (>14 mm at Ultrasound Scan). Women were treated with a constant dose of FSH. The starting dose of FSH was individually adjusted according to age, Body Mass Index (BMI), and Antral Follicle Count (AFC), and began on the 6th or 7th day of the cycle. Ultrasound and biological assessment were performed after 5 days of FSH stimulation. Ovulation was triggered by human chorionic gonadotropin (hCG) injection followed by IUI performed 24–36 h after. Patients were referred to ART if they did not begin a pregnancy:

- After 12 months of expectative management or 6 stimulated cycles.
- After 6 months of expectative management or 3 stimulated cycles according to age (>40 years), ovarian reserve assessed by ultrasound AFC (AFC 6–8), and length of infertility (>36 months).

Intent to treat analysis for post-operative pregnancy rates was performed to reflect, more accurately, current practice. So, lost of follow-up patients were considered as not pregnant just before ART and were, at this time, dropped out of the study.

Data collections and analysis

Data on historic, physical examination, history of infertility, surgery, postoperative follow-up and subsequent fertility were collected prospectively for all endometriotic and infertile patients in our database.

Diminished ovarian reserve (DOR) was defined as: FSH >14 UI/L or AMH <1 ng/ml, or AFC <8; and/or previous IVF attempt (possibly in another centre) with retrieved oocytes <4.

A spontaneous pregnancy was defined by a β-hCG level above 25 IU/L. The mean delay to conceive spontaneously, or after superovulation with or without IUI was calculated from the date of surgery to blood HCG date. The mean delay to conceive after IVF was expressed by the number of started cycles, including all cycles whatever their outcomes: (i) cancelled, (ii) triggered, (iii) no embryo transfer, (iv) fresh or frozen-warmed embryo transfer.

Statistical analyses were performed using Stata software (Stata, version 11.0, StatCorp., LP, USA, www.stata.com). Descriptive data analysis used Student *t* test, and variance analysis used ANOVA for continue variables when comparing more than two categories (two-way ANOVA). The chi-squared test or Fisher exact test was used for qualitative variables when $n < 5$. Pearson's regression analysis was used to determine correlations. Bilateral tests were considered significant if $p < 0.05$.

A univariate analysis was performed to study explanatory factors between pregnant and non-pregnant patients. To explain the occurrence of non-IVF pregnancy, we performed a multivariate analysis using stepwise logistic regression. We adjusted for

potential confounding variables that were significant ($p < 0.05$) or tending towards significance ($p < 0.1$) in the univariate analysis.

Results

During the study period, 315 patients with SUP met inclusion criteria and were enrolled. The flow chart is shown in Fig. 1. In all, 315 women had subsequent fertility management. Of these, 133 (42.3%) women had non-IVF pregnancy. Post-operative ovarian stimulations (pOS) were undertaken in 114 (36.2%) women. Among the women with pOS, 51 (38.3%) women had superovulation and 63 (47.3%) had superovulation and IUI. A pregnancy was achieved after pOS in 66 women (57.9% of pOS, or 21% when considering the overall population). Of the 201 women without pOS, 67 women (33%, representing 21.3% of the global population) became spontaneously pregnant.

The non-ART mean time to conceive was 6 months and 6 days (±3 months and 12 days). The mean number of pOS cycles was 2.3 ± 1.4.

Considering non-pregnant women after surgery, 182 were referred to ART attempts. Of these, 19 women (10.4%, representing 6% of the global population) were lost of follow-up, hence considered not pregnant to the end, and dropped out of the study. So, 163 women had ART attempts (representing 556 started cycles). Of these 101 women became pregnant (62%, representing 32% of the global population). The mean number of started cycles to obtain a pregnancy with ART was 2.8 (±1.8).

Pre-operative characteristics of pregnant and non-pregnant women after surgery were summarized in Table 1. No difference was observed according to age, length of infertility, Body Mass Index (BMI), the rate of previous pregnancy, and the pre-operative ovarian stimulation rate. Diminished ovarian reserve was significantly higher in the non-pregnant women group (8.3% versus 19.1%, $p = 0.01$). Non-pregnant women had a significant lower rate of previous miscarriage as compared with pregnant women (3.5% versus 9%, $p = 0.02$). Per and postoperative characteristics of pregnant and non-pregnant women are shown in Table 2. According to ASRM staging, in minimal to mild endometriosis ($N = 202$) and in moderate to severe endometriosis ($N = 113$), pregnancy rates were not different:44.5% ($N = 90$) versus 38% ($N = 43$), respectively. The mean EFI score was higher in the group of postoperative pregnant women (7.7 versus 7.2, $p = 0.02$). Postoperative ovarian superovulation with or without IUI was higher in pregnant than in non-pregnant women (49.2% versus 26.7%, $p < 0.01$). According to the mode of pOS, Intra Uterine Insemination did not show any benefit for pregnancy in the pOS group (22% after superovulation versus 27.2% after superovulation and IUI).

In the multivariate analysis, after adjusting confounding variables, pOS was associated with a 2.5 folds' increase in the incidence of pregnancy (adjusted OR 2.504, 95% CI 1.537–4.077). Diminished ovarian reserve was associated with a lower incidence of pregnancy (OR 0.420, 95% CI [0.198–0.891]) (Table 3).

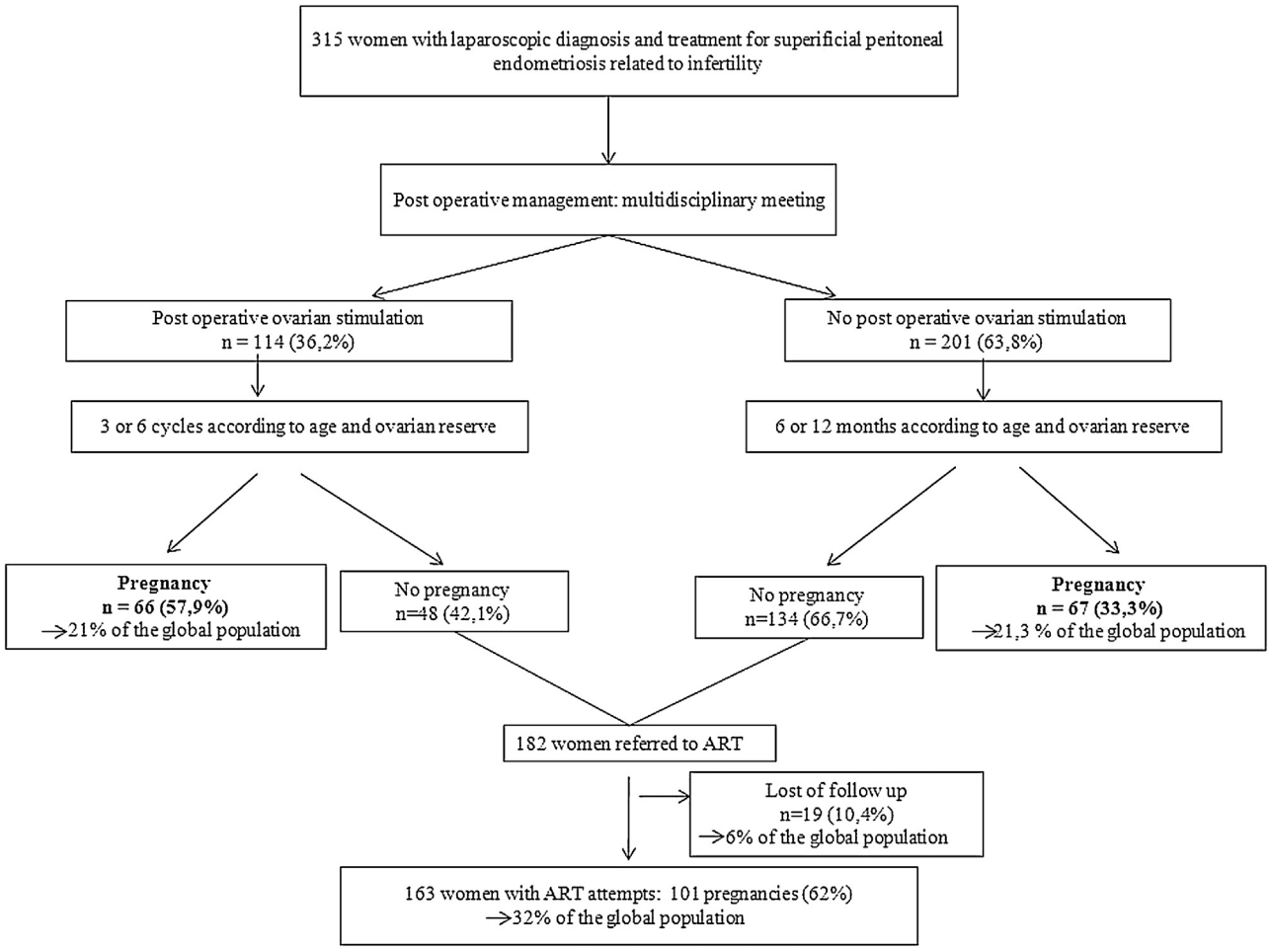

Fig. 1. Flow chart. ART: Assisted Reproductive Technology.

Table 1
Per-operative characteristics of the two groups according to the occurrence of pregnancy after surgery.

	Pregnancy (n = 133)	No pregnancy (n = 183)	p
Mean age in years (min–max)	32.2 (23–43)	32.5 (21–43)	0.77
Mean BMI (min–max)	23.07 (15–34)	23.27 (15–38)	0.64
Previous pregnancy n (%)	31 (23.3%)	58 (24%)	0.16
Previous live birth n (%)	26 (19.5%)	35 (14.4%)	1
Miscarriage n (%)	5 (3.7%)	22 (9%)	0.02
Caesarean section n (%)	8 (6%)	11 (6%)	0.86
Mean length of infertility (min–max)	38 (6–96)	39 (6–192)	0.71
Diminished ovarian reserve (DOR) n (%)	11 (8.3%)	35 (19.1%)	<0.01
Pre operative ovarian superovulation (±IUI) n (%)	87 (66.6%)	121 (66.1%)	0.92

n: number of patients, IUI: Intra Uterine Insemination.

Table 2
Per-operative and post operative characteristics of the two groups according to the occurrence of pregnancy after surgery.

	Pregnancy n = 133	No pregnancy n = 183	p
Mean rAFS score (min–max)	6.4 (1–70)	8.1 (1–114)	0.22
I–II ASRM stage n (%)	90 (67.6%)	112 (61.5%)	0.17
III–IV ASRM stage n (%)	43 (32.3%)	70 (38.4%)	0.17
Adnexal adhesions n (%)	62 (46.9%)	81 (44.26%)	0.57
Douglas Pouch SUP n (%)	82 (62.1%)	120 (65.5%)	0.77
Uterin vesical fold SUP n (%)	45 (34%)	67 (36.6%)	0.82
Ovarian Fossa SUP n (%)	77 (58.3%)	109 (59.5%)	0.92
Ovary cortex SUP n (%)	36 (27.2%)	50 (27.3%)	1
Utero sacral SUP n (%)	42 (32.6%)	64 (34.9%)	0.72
More than 2 peritoneal sites n (%)	68 (51.5%)	112 (61.2%)	0.16
Mean least function score (min–max)	7.24 (0–8)	6.9 (0–8)	0.05
Mean EFI score (min–max)	7.7 (3–10)	7.2 (3–10)	0.02
Complete surgery n (%)	127 (96.2%)	173 (94.5%)	NS
Post operative ovarian superovulation (±IUI) n (%)	65 (49.2%)	49 (26.7%)	<0.01

N: number of patients, SUP: Superficial Peritoneal Endometriosis, rAFS: revised American Fertility Society, ASRM: American Society of Reproductive Medicine, EFI: Endometriosis Fertility Index, IUI: Intra Uterine Insemination.

Table 3
Multivariate analysis: predictive factors for spontaneous pregnancy after laparoscopic surgery.

Variables	Adjusted Odds ratio	95% CI
Endometriosis Fertility Index	1.167	0.985–1.382
Post-operative ovarian superovulation (±IUI)	2.504	1.537–4.077
Diminished ovarian reserve	0.420	0.198–0.891
Previous miscarriage	0.823	0.683–1.958

IUI: Intra-uterine Insemination.

Discussion

Main findings

In our experience, post-operative ovarian stimulation was associated with an increased pregnancy rate after laparoscopic diagnosis and treatment for superficial peritoneal endometriosis related infertility. Our findings were in line with previous studies [20–27] and inconsistent with others [28,29]. However, available data have shown major heterogeneities. Effectively, several reports included different populations such as endometriosis, unexplained infertility, and pelvic adhesions. Using ASRM staging rather than different phenotypes of endometriotic lesions (SUP, DIE, endometrioma with or without bowel involvement), results might not be so useful in clinical practice. Moreover, the discrepancy between ovarian stimulation protocols (clomifene citrate, letrozole, FSH, combined treatment, with or without IUI) may have influenced subsequent results.

Considering the mean time to conceive after surgery in our study, and previous published data, women may benefit of stimulated ovarian cycles to enhance pregnancy rate [21–27].

For minimal or mild endometriosis (that may be a proxy of superficial peritoneal disease), several authors [22,28,30–33] reported ovarian stimulation benefits for pregnancy. In contrast to our results, some authors found an added value for combined IUI and COS management versus IUI or COS alone [28,32]. Therefore, added IUI with ovarian stimulation benefit compared to ovarian stimulation alone remained a matter of debate [29].

Considering moderate to severe endometriosis associated infertility, operative laparoscopy could be considered to increase spontaneous pregnancy rate [34], but clear data on post-operative management were missing. Therefore the benefit of superovulation and IUI in moderate to severe endometriosis remains unclear [20].

We found that diminished ovarian reserve was associated with a lower incidence of non-ART pregnancy. Our result is in accordance with other studies that have reported lower non-ART pregnancy [35,36]. However the management of DOR and endometriosis related to infertility remains a matter of debate because of the heterogeneity of DOR definition and the poor benefit of ART management [37].

Strengths and limitations

Our study was the first to consider the phenotype of endometriosis rather than the ASRM staging. Our results provide new data about the postoperative management of SUP endometriosis related infertility. The multivariate analysis for pregnancy after surgery strengthens the added value for postoperative stimulation.

While assignment of patients for postoperative management was decided in multidisciplinary meeting the retrospective design of our study cannot ruled out a selection bias for post-operative ovarian stimulation.

As only patients with laparoscopic diagnosis and treatment were included, the benefit of ovarian stimulation for endometriosis related to infertility without surgery remains unclear.

In our study, only recombinant or urinary gonadotrophins were used. Therefore our results may not support other protocols.

Interpretation

Peritoneal fluid and cavity microenvironments in women with superficial peritoneal endometriosis were shown to be modified, and may reduce fertility by different mechanisms [38,39]. Endometriosis related pelvis adhesions may reduce fallopian tubes and ovarian mobility. These mechanisms could explain advantages of adhesiolysis as well as the complete treatment of SUP [15]. Indeed, potential negative effects on ovarian steroidogenesis and folliculogenesis of endometriosis [40] may explain the ovarian stimulation benefits after surgery. Effectively, a higher rate of luteinized unruptured follicle syndrome and occult ovarian failure have been observed in women with unexplained or minimal to mild endometriosis related infertility [41,42]. Ovarian stimulation could be useful to correct these subtle disorders of ovarian dysfunction.

While peritoneal lesions could have a negative impact on the fecundability, the SUP endometriosis laparoscopic treatment benefit, in order to improve pregnancy rate with super ovulation and IUI, remains unclear. Omland et al. found a significantly lower total pregnancy rate in minimal to mild endometriosis group compared with unexplained infertility group [43] while Matorras et al. observed similar pregnancy rates in normal women and in women with minimal endometriosis [44]. In another study Werbrouck et al. found that COH and IUI shortly after laparoscopic excision of endometriosis was as effective as COH and IUI in patients with unexplained subfertility [21].

None of the studies evaluated the existence of sexual dysfunction. Several studies suggested that both women with infertility [45] and women with endometriosis [46] had more sexual dysfunction. This issue should be included in the postoperative management of women with endometriosis related infertility.

Conclusion

After laparoscopic surgery for peritoneal superficial endometriosis related infertility, ovarian stimulation improved pregnancy rate, while diminished ovarian reserve had a worse prognosis for pregnancy.

Conflict of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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The study was not financially supported by any foundation or organization.

Ethical approval

No formal Ethical Approvement from Paris XIII University Centre medical ethics committee was necessary for the study.

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