European Journal of Obstetrics & Gynecology and Reproductive Biology 211 (2017) 182–187

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

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

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ARTICLE INFO

Article history:
Received 15 January 2017
Accepted 4 March 2017
Available online xxx

Keywords:
Superficial peritoneal
Endometriosis
Fertility
Surgery
Ovarian stimulation

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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http://dx.doi.org/10.1016/j.ejogrb.2017.03.008
0301-2115/

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