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Original Article

Factors associated with pregnancy after in vitro fertilization in infertile patients with posterior deep pelvic endometriosis: A retrospective study

C. Rubod[a,d,*], A. Fouquet[a,b], S. Bartolo[a], J. Lepage[a,b], A. Capelle[b], C. Lefebvre[b], E. Kamus[c], D. Dewailly[b,d], P. Collinet[a,d]

[a] Service de chirurgie gynécologique, Hôpital Jeanne de Flandre, CHRU de Lille, 59 037 Lille, France
[b] Service de Médecine de la Reproduction, Hôpital Jeanne de Flandre, CHRU de Lille, 59037 Lille, France
[c] Service de radiologie, Hôpital Jeanne de Flandre, CHRU de Lille, 59037 Lille, France
[d] Faculté de Médecine H. Warembourg, Université de Lille, France

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ABSTRACT

Introduction: The management of posterior deep endometriosis is not consensual. This is due to a great heterogeneity of data from the literature. Many series were small and overall, predictors of pregnancy were not all included and analyzed by multivariate analysis. We conducted this study to evaluate the factors associated with pregnancy during the first two in vitro fertilization (IVF) attempts in infertile women with posterior deep endometriosis.
Material and methods: 230 women were included in this retrospective observational study, between January 1st, 2007 and September 30th, 2013, at the University Hospital of Lille. A large set of variables were recorded and their association with the chance of pregnancy was analyzed by multivariate analysis (MVA), including patients' features, endometriosis items, surgery procedures and IVF data.
Results: After 2 IVF attempts, 48.7% of the 230 women achieved a pregnancy, including 39.1% of ongoing pregnancies. Logistic regression analysis retained five variables significantly associated to the chance of pregnancy: oocyte retrieval number (OR = 0.468 (0.296–0.739) $p = 0.001$), age (OR = 0.888 (0.811–0.974) $p = 0.011$), single embryo transfer number (OR = 1.494 (1.036–2.153) $p = 0.031$), presence of a recto-uterine nodule (OR = 0.454 (0.235–0.877) $p = 0.019$) and IVF technique (OR = 0.509 (0.272–0.951) $p = 0.034$).
Conclusion: The presence of a recto uterine nodule is associated with a lower chance of pregnancy after IVF. It has to be checked by prospective studies whether the finding of a recto-uterine nodule whose pejorative effect has not been reported so far should encourage to perform surgery before IVF in patients with deep endometriosis.

Introduction

The frequency of endometriosis is estimated at about 10% of women in the general population and 25–50% of infertile women [1,2]. Endometriosis is associated with a primary or secondary infertility in 30–50% of cases [1,3] and the risk of infertility is 20 times higher in women with endometriosis compared to the general population [4]. The use of assisted reproductive techniques (ART), and particularly in vitro fertilization (IVF) is common.

With regard to the pain associated with endometriosis, it is recognized that the surgery improves symptoms and quality of life [5–7], particularly in case of endometriosis with bowel involvement [8]. However, surgery is associated with specific complications, estimated between 2.1 and 4.6% depending on the study [5].

Regarding fertility, the Cochrane review of 2010 and the consensus of the World Endometriosis Society in Montpellier in 2011 recommend a surgical management to improve fertility in American Society of Reproductive Medicine (ASRM) stages I and II [7,9]. Data from the literature are however contradictory about the benefits of surgery on fertility in stages III and IV. Some authors

Abbreviations: AMH, anti Mullerian hormone; ART, assisted reproductive techniques; CS, complete surgery; ICSI, Intra Cytoplasmic Sperm Injection; IS, incomplete surgery; IVF, in vitro fertilization; MDM, multidisciplinary meetings; MRI, magnetic resonance imaging; MVA, multivariate analysis; NS, no surgery; US, utero sacral ligaments.

* Corresponding author at: Hôpital Jeanne de Flandre – CHRU Lille, 1 rue Eugène Avinée, 59037 Lille Cedex, France.
E-mail address: chrystele.rubod@chru-lille.fr (C. Rubod).

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showed that previous surgery improved spontaneous or post-ART fertility [7,10–13], while others showed no difference [14].

The posterior deep endometriosis has been extensively studied because it frequently causes both severe pain and infertility [15]. Its definition according to Chapron et al. [16] requires lesions of the utero-sacral ligaments and/or vagina and/or bowels. Its current management in infertile women is not consensual. Some authors [17,18] recommended surgery after two IVF failures in colorectal deep endometriosis. The question arises if surgery before IVF is beneficial for fertility. No benefit was shown by some authors [19,20], while other studies have shown that colorectal resection improved fertility [21–23]. Nevertheless, series were small and heterogeneous and possible confounders were not always taken in account.

Therefore, the analysis of the literature about fertility management in deep endometriosis is not conclusive. The objective of this study was to search retrospectively for independent factors associated with pregnancy after the first two IVF attempts in patients with posterior deep endometriosis, using multivariate analysis in order to eliminate the confounding effects of some variables. We hypothesized that such approach would help in deciding the best strategy and in counseling patients. We focused more particularly on the treatment used prior to IVF, i.e., no, incomplete or complete surgery, according to the decision taken at the time of Multidisciplinary Meetings (MDM) and based on an established protocol in our center.

Material and methods

Patients

This is a retrospective observational single center study. We included all patients referred between January 1, 2007 and September 30, 2013 to the Lille Regional University Hospital for primary or secondary infertility, lasting at least one year and related to posterior deep endometriosis, who had one or two IVF attempts.

All patients gave their consent for the use of their clinical information for medical research before the treatment.

Exclusion criteria were: isolated anterior localization of deep endometriosis, use of egg donation, patients who were operated between the first two IVF attempts and patients with a recurrence of their deep endometriosis after complete surgery before IVF.

The diagnosis of deep endometriosis has been made by Magnetic Resonance Imaging (MRI) in all patients and confirmed by laparoscopy with pathological examinations in operated patients (151 patients over 230). All patients underwent pelvic MRI with rectal and vaginal contrast, and all MRIs were read by radiologists of the center to evaluate the location of the deep endometriosis, to measure endometriomas and deep endometriosis nodules and to assess the presence of internal or external adenomyosis, as well as the presence of salpinx. The MRI was prescribed when endometriosis was suspected, whereas the patient had symptoms of endometriosis or when endometriosis was suspected on the ultrasound made for every woman who underwent infertility check-up.

The posterior deep endometriosis was defined as lesions of the torus, the uterosacral ligaments (US), the recto-uterine space, the rectovaginal septum, and/or the bowels. The classification according to the ASRM was used only in patients who were operated, since this classification is not appropriate to stage endometriosis on MRI only [1].

Therapeutic strategy

For all patients, therapeutic strategy was based on an established protocol of care and validated during a Multidisciplinary Meeting (MDM) [24]. The decision lied on clinical, biological and MRI items, particularly symptoms, patient's age, duration of infertility, ovarian reserve, pelvic surgical history, accessibility to ovaries for oocyte retrieval and location and extent of the deep endometriosis at MRI. Our protocol, following current recommendations [5–7,9], was to propose a complete surgery (CS) for patients with symptomatic endometriosis after failure of a well conducted medical treatment (GnRH agonists during 3–6 months and pain killers) and an incomplete surgery (IS) in non-symptomatic patients when the goal was only to facilitate IVF conditions (large endometriomas, salpinx, ovaries non reachable for oocyte retrieval). No surgery (NS) was performed in the remaining patients, who were asymptomatic and which endometriosis did not affect the IVF conditions. Complete surgery consisted on removing all the endometriosis lesions, and incomplete surgery consisted on a kystectomy and/or a salpingectomy and/or an adhesiolysis. Complications of surgery were evaluated per-operatively, early post-operatively and late post-operatively.

ART features

Data collection of the ART course was made from the INFOFIV database of the Lille University Hospital. Female infertility evaluation included hormonal biological assessment between the 2nd and the 5th day of the cycle, pelvic endovaginal ultrasound with antral follicular count (AFC) and hysterosalpingography. Male semen analysis included spermocytogramme and sperm migration test.

IVF, either conventional or with Intra Cytoplasmic Sperm Injection (ICSI), was performed in all patients. Patients were stimulated according to conventional protocols, using either long or short GnRH agonists, or GnRH antagonists protocols. Gonadotropin doses for stimulation ranged from 75 to 450 IU/day depending on the age, body mass index (BMI) and ovarian reserve. The number of embryos replaced was determined based on the patient's age, the course of infertility, the embryo quality and the choice of the couple. Oocyte retrieval was canceled in case of poor response as defined by the presence of less than three follicles measuring 17 mm or more for women under 35 years old and less than 5 follicles measuring 17 mm or more for women over 35 years old, at the time of the triggering decision. Embryo transfer was canceled in case of absence of oocyte or failure of fertilization or poor quality of the embryo cohort.

Pregnancy is defined by a positive pregnancy test as positive HCG or the presence of an intra-uterine gestational sac.

We limited our study to the first two IVF attempts, since our strategy is to re-consider the surgical indication after 2 IVF failures.

Statistical analysis

Statistical analyzes were performed using the software Statistical Package for Social Sciences (SPSS 22.0 for Windows), IBM, New York, USA. Results are presented as means with standard deviations for quantitative variables and as frequency and percentage for categorical variables. The chi-square test was used for categorical variables. The Anova test was used for quantitative variables whose distribution was normal. Non-parametric tests (Mann–Whitney or Kruskall–Wallis test for comparison of 2 groups or more, respectively) were used for variables not following a normal distribution.

MVA was performed by logistic regression applied to the whole group, using as dependent variable the occurrence of at least one pregnancy (no = 0, yes = 1). If the explicative variables were continuous the linearity of the relation was tested. For each variable selected by the analysis, the odds risk (OR) with 95% confidence interval (CI) was computed. A p value <0.05 was considered statistically significant.

Ethical approval statement

Not necessary because it is a retrospective study, and all patients signed a consent allowing the use of their data.

Results

After 1 or 2 IVF attempts, 48.7% of the 230 patients achieved a pregnancy, including 39.1% of ongoing pregnancies. 90 women had only one oocyte retrieval, and 52 of them were pregnant at the first IVF attempt. 87 women gave birth to 105 children. By bivariate analysis, comparison of patients who were pregnant to those who did not achieve pregnancy retrieved five factors that were significantly associated with the chance of pregnancy (Tables 1–3). These five factors were age (Table 1), the presence of a recto-uterine nodule (Table 2), the IVF technique (i.e., ICSI or not), the number of oocyte retrievals per patient and the number of single embryo transfer (Table 3). A trend without reaching significance was found for 4 other factors: the infertility duration (Table 1), the serum AMH level (Table 1), the maximum size of endometriotic cysts (Table 2) and the total number of embryos (Table 4).

There was no significant difference between groups pregnant and not pregnant whether the recto-uterine nodule has been operated or not, nor depending on its size nor its association with a bowel involvement and/or with internal or external adenomyosis. Other endometriosis characteristics were not significantly different between these 2 groups. Within each group, the percentage of NS, IS and CS was similar (Table 3). We found that in the CS group 54.7% of the patients became pregnant, vs 46.0% in the IS group and 45.6% in the NS group (NS).

A MVA was then performed in order to identify, among the variables with a p value <0.1 (Tables 1–4), those significantly and independently associated to the occurrence of at least one pregnancy. By logistic regression, five significant variables were retained (oocyte retrieval number, age, single embryo transfer number, presence of a recto-uterine nodule and IVF technique) with OR (CI) of 0.468 (0.296–0.739), 0.888 (0.811–0.974), 1.494 (1.036–2.153), 0.454 (0.235–0.877) and 0.509 (0.272–0.951), respectively (p = 0.001, 0.011, 0.031, 0.019 and 0.034, respectively).

Discussion

Main findings

The cumulative pregnancy rate in our population after the first 2 IVF attempts (48.7%) was in the range of previously reported series, i.e., 40–60%. However, populations are not always comparable, endometriosis stages are variable and strategies are different [13,17,25–27]. This rate was 50.0% (38.9% of ongoing pregnancies) for patients with gastrointestinal involvement.

Table 1
Population studied.

	Total n = 230	NP n = 118	P n = 112	p
Age (years)	31.1 ± 3.6	31.8 ± 3.5	30.3 ± 3.4	0.001
BMI (kg/m^2)	23.2 ± 4.4	23.5 ± 4.8	23.0 ± 4.0	0.48
Gravidity	0.2 ± 0.5	0.1 ± 0.5	0.2 ± 0.5	0.72
Parity	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.2	0.14
Infertility period (months)	42.3 ± 22.6	45.1 ± 24.3	39.4 ± 20.2	0.055
Tobacco (cigarettes per day)	2.3 ± 4.9	2.56 ± 5.5	1.9 ± 4.3	0.41
AMH (ng/ml)	3.7 ± 2.8	3.4 ± 2.5	4.0 ± 3.1	0.089
AFC	19.1 ± 12.2	18.2 ± 11.5	20.0 ± 13.0	0.31

BMI: body mass index; AMH: anti-Mullerian hormone; NP: not pregnant; P: pregnant.

There is no difference in regency rate between women having CS or NS, 31.5% and 32.4% respectively. This result differed from those of Bianchi et al. [13] that found an improvement of IVF pregnancy rates after extensive laparoscopic excision of deep infiltrative endometriosis (24% vs 41%).

Our MVA indicated that most of the factors associated with pregnancy at the end of the first 2 IVF attempts were known or expected factors: the age, the number of oocyte retrievals and transfer per patient, and the ART used. Conversely, we report for the first time that the presence of a recto-uterine nodule seems to be a pejorative factor on the pregnancy rate after IVF, independently from other factors, subject to the limitations of the study.

In our logistic analysis, the strongest association with the chance of pregnancy was the number of oocyte retrievals per patient and it was negative (i.e., OR < 1) This was expected as the number of oocyte retrievals per patient was significantly higher in patients who did not achieve pregnancy compared with those who got pregnant. Indeed, we have included in the analysis oocyte retrievals not followed by transfer, whether for lack of oocytes at oocyte retrieval, or for failure of fertilization, or for bad quality embryos. These circumstances have a poor prognosis for subsequent attempts, which explains the lower rate of pregnancy. This explains that the transfer number was also included in our multivariate model. Likewise, the ART used was included in this model. Indeed, patients who underwent IVF were significantly more likely to become pregnant compared to those who underwent IVF-ICSI. This can be explained by the higher frequency of sperm alterations that justified the use of ICSI.

In our MVA, we also confirmed the negative effect of age, already demonstrated in several studies. Beyond a most often fixed threshold at 35 years, there is a significant decrease in pregnancy rate and an increase in miscarriage rate [21,22,26,28,29]. This emphasizes the need for an early diagnosis and management.

Unexpectedly, the presence of a recto-uterine nodule on the preoperative exams, was significantly associated, and independently from other factors, with a negative effect on IVF pregnancy rate. To our knowledge, this has never been reported in the literature. We have not found bias such as bowel involvement or presence of internal or external adenomyosis. Our study does not allow us to clearly explain this association. Obviously, this finding will require further confirmation and explanation.

Our MVA did not retain certain parameters that we thought being possibly associated with the chance of pregnancy. This was the case for serum AMH level which tended to be higher in patients who got pregnant but without reaching significance (p = 0.09). As expected, serum AMH levels were significantly lower in patients treated by CS (data not shown) but this had no impact on pregnancy rate. Gonadotropin suppression therapy prior to surgery in these patients rather than ovarian damage might explain this paradox. In a population of patients with colorectal endometriosis, Ballester et al. [17] observed that an AMH level <2 ng/ml was significantly more frequent in the group of patients who did not achieve pregnancy compared to the group of patients who achieved pregnancy in IVF-ICSI (p = 0.03). Among patients aged 35 and over, Sahmay et al. [30] found an average AMH value significantly lower in the patient group who did not achieve pregnancy compared with those who had been pregnant (p < 0.001). However, in agreement with our findings, no study has shown that serum AMH level was directly and independently related to the chance of pregnancy.

Similarly, in our analysis, the extent of the endometriosis did not affect the chance of pregnancy. Neither the size of the deep endometriosis lesion on MRI nor the presence of a bowel involvement, common in our population (54.3%), were associated with pregnancy rate. These results are discordant with previous studies that again did not follow a multivariate approach.

Table 2
Characteristics of deep pelvic endometriosis.

	Total $n = 230$ (%)	NP $n = 118$ (%)	P $n = 112$ (%)	p
Location of DPE				
Torus and uterosacral ligaments	204 (88.7)	108 (90.8)	96 (86.5)	0.33
Recto-uterine	67 (29.1)	43 (36.1)	24 (21.6)	0.02
Rectovaginal	85 (37.0)	41 (34.5)	44 (39.6)	0.39
Recto-uterine and/or rectovaginal	132 (57.4)	70 (58.8)	62 (55.9)	0.73
Vesicouterine	38 (16.5)	21 (17.6)	17 (15.3)	0.59
Internal adenomyosis	27 (11.7)	15 (12.6)	12 (10.8)	0.64
External adenomyosis	73 (31.7)	40 (33.6)	33 (29.7)	0.56
Gastrointestinal involvement	125 (54.3)	63 (52.9)	62 (55.9)	0.57
Size of EPP nodule	28.2 ± 14.7	28.0 ± 16.9	28.5 ± 14.4	0.81
Max endometriosis cyst size	24.5 ± 22.5	22.0 ± ± 19.6	27.2 ± 25.1	0.08
Grade ASRM				0.87
1	15 (6.5)	9 (7.6)	6 (5.4)	
2	40 (17.4)	19 (16.0)	21 (18.7)	
3	61 (26.5)	31 (26.3)	30 (26.8)	
4	114 (49.6)	59 (50.0)	55 (49.1)	

DPE: deep pelvic endometriosis; MRI: magnetic resonance imaging; ASRM: American Society of Reproductive Medicine; NP: not pregnant; P: pregnant.

Table 3
Characteristics of the surgery.

	Total $n = 230$	NP $n = 118$	P $n = 112$	p
Complete surgery	64 (27.8)	29 (24.6)	35 (31.2)	0.26
Incomplete surgery	88 (38.3)	48 (40.7)	40 (35.7)	0.80
No surgery	78 (33.9)	41 (34.7)	37 (33.0)	0.80
Characteristic of surgery				
Excision of a DPE nodule	77 (45.3)	40 (43.5)	37 (47.4)	0.52
Adnexal surgery	112 (65.8)	54 (58.7)	58 (74.3)	0.12
Tubal surgery	49 (29.0)	27 (29.4)	22 (28.6)	0.92
Digestive surgery				
Rectal shaving	9 (6.0)	5 (4.2)	4 (3.6)	0.76
Bowel resection	23 (15.2)	7 (5.9)	16 (14.3)	0.12
Colpectomy	24 (14.1)	14 (15.2)	10 (12.8)	0.57

NP: not pregnant; P: pregnant.

Table 4
Characteristics of in vitro fertilization.

	Total $n = 230$	NP $n = 118$	P $n = 112$	p
Features IVF attempts				
IVF	171 (74.3)	79 (66.4)	92 (82.9)	0.012
IVF-ICSI	59 (25.6)	40 (33.6)	19 (17.1)	
Number punctures per patient	1.8 ± 0.8	1.9 ± 0.8	1.6 ± 0.6	0.003
Total cumulative oocytes	13.7 ± 8.1	13.9 ± 8.9	13.4 ± 7.5	0.72
Total number of embryos	6.2 ± 4.1	5.7 ± 4.3	6.8 ± 3.9	0.056
Number of fresh embryo transfer	1.4 ± 0.6	1.3 ± 0.7	1.5 ± 0.5	0.20
Number of FET per patient	0.5 ± 0.9	0.5 ± 1.0	0.5 ± 0.9	0.86
Number of embryo transferred (ET + FET) per patient				
1 embryo	0.6 ± 0.9	0.5 ± 0.8	0.8 ± 1.0	0.038
2 embryos	1.2 ± 1.0	1.2 ± 1.2	1.1 ± 0.7	0.78
3 embryos	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2	0.49
Complication of IVF				
Ovarian hyperstimulation	16 (7.0)	5 (4.2)	11 (9.9)	0.10
Hemorrhage	3 (1.3)	1 (0.8)	2 (1.8)	0.53
Infection	2 (0.9)	2 (1.7)	0	0.17
Thrust endometriosis	1 (0.4)	1 (0.8)	0	0.32

IVF: in vitro fertilization; ICSI: Intra-Cytoplasmic Sperm Injection; NP: not pregnant; P: pregnant.

Stepniewska et al. [23] reported a negative impact of digestive lesions on spontaneous or IVF fertility and they observed an improvement of fertility after complete surgery of digestive endometriosis, with bowel resection and anastomosis. Other authors have reported the negative impact of the presence of adenomyosis and gastrointestinal lesions [21,22]. In our study the extent of endometriosis does not affect the chances of pregnancy, except for recto-uterine nodules, as discussed above.

This study also included the role of treatment prior to IVF, although it was not designed to address specifically this issue. To demonstrate a potential benefit or not of surgery would require a comparative prospective study. In our series, pregnancy rate was not different depending on whether the patient was operated or not and the type of surgery. Moreover, our MVA did not obviate any association between the prior-IVF treatment and the chance of pregnancy. This can be explained by our management based on decision made at MDM and this result validates a posteriori our indications, i.e., to recommend surgery for symptomatic patients or for adnexal pathologies hampering attainment of oocyte retrieval and to prefer IVF immediately in minimally symptomatic patients. The situation has to be reassessed after two IVF failures. It has to be noted that the rate of surgical complications was comparable to literature data [21,22,31,32] with few consequences.

Strength and limitations

The single-center and observational nature of our study has its limitations. We have studied the patients who attempt IVF, and did not look for spontaneous pregnancies. We have not studied the impact of surgery on symptoms. In fact these data were difficult to assess objectively in our study. However, it has already been shown in many studies that surgery improves the symptoms and quality of life in endometriosis [6,8,9]. We studied all stages of deep endometriosis, but our population included mostly stages III and IV. Conversely, our study has some strength: we studied a large population with strict inclusion criteria, assessed over a period of $6^1/_2$ years and with a very consensual therapeutic strategy through MDMs [24]. Surgeons are very specialized, with an activity essentially centered on surgery of infertility and in particular endometriosis, with collaboration with visceral surgeons and urologists also specialized, which meets the current recommendations [9].

Conclusion

In conclusion, results from this study on an important series suggest for the first time that the presence of a recto-uterine nodule is pejorative on pregnancy rate, and confirm the known associated factors such as age and IVF characteristics. Therapeutic strategies that were proposed in the MDMs yielded the same

chances of pregnancy for all patients. These results allow a better counseling of the patients with deep pelvic endometriosis.

Key message

The presence of a recto-uterine nodule is pejorative on pregnancy after IVF.

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Conflict of interest

None.

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