

High postoperative fertility rate following surgical management of colorectal endometriosis

Horace Roman^{1,*}, Isabella Chanavaz-Lacheray¹, Marcos Ballester^{2,3,4}, Sofiane Bendifallah^{2,3,4}, Salma Touleimat¹, Jean-Jacques Tuech⁵, Marilena Farella¹, and Benjamin Merlot⁶

¹Expert Center in the Diagnosis and Multidisciplinary Management of Endometriosis, Rouen University Hospital, 76031 Rouen, France

²Department of Obstetrics and Gynecology, Tenon University Hospital, Assistance Publique Hôpitaux de Paris, Paris, France ³GRC-6 UPMC: Centre Expert en Endométriose (C3E), Université Pierre et Marie Curie, Paris, France ⁴Unité INSERM UMR_S 938, Université Pierre et Marie Curie, 75020 Paris, France ⁵Department of Surgery, Rouen University Hospital, 76031 Rouen, France ⁶Clinique Tivoli-Ducos, 33000 Bordeaux, France

*Correspondence address. Clinique Gynécologique et Obstétricale, CHU «Charles Nicolle», 1 rue de Germont, 76031 Rouen, France. Tel: +33-232-888-754; Fax: +33-235-981-149; E-mail: horace.roman@gmail.com

Submitted on March 1, 2018; resubmitted on May 9, 2018; accepted on May 23, 2018

STUDY QUESTION: What are fertility outcomes in patients surgically managed for large deep endometriosis infiltrating the rectum who intend to get pregnant postoperatively?

SUMMARY ANSWER: Surgical management for rectal endometriosis is followed by high pregnancy rates, with a majority of natural conceptions.

WHAT IS KNOWN ALREADY: Optimal management such as surgery versus first-line ART for patients with severe deep endometriosis who desire pregnancy is not defined.

STUDY DESIGN, SIZE, DURATION: The study included the patients enrolled in ENDORE randomized trial who attempted pregnancy after the surgery. From March 2011 to August 2013, we performed a two-arm randomized trial, enrolling 60 patients with deep endometriosis infiltrating the rectum up to 15 cm from the anus, measuring more than 20 mm in length, involving at least the muscular layer in depth, and up to 50% of rectal circumference. Postoperative follow-up was prolonged in 55 patients recruited at Rouen University Hospital, and varied from 50 to 79 months. No women were lost to follow-up.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Patients had either conservative surgery by shaving or disc excision, or radical rectal surgery by segmental resection. One gynecologist experienced in deep endometriosis surgery performed all the procedures, assisted when required by three general surgeons experienced in colorectal surgery. Institutional review board approval was obtained to extend postoperative follow-up to 10 years after the surgery. Among patients enrolled at Rouen University Hospital, women who intended to get pregnant after surgery were selected and followed up postoperatively every 6 months for 2 years, then every year. Pregnancy intention, fertility outcomes, conception mode, endometriosis recurrences and digestive and urinary outcomes were rigorously recorded. The primary outcome was postoperative pregnancy rate. Secondary outcomes were conception mode, the delay to conception from the day of surgery and the day when hormonal treatment was stopped, and delivery rate. Kaplan Meier curves were used to estimate the probability of conception after surgery.

MAIN RESULTS AND THE ROLE OF CHANCE: Among the 55 patients enrolled at Rouen University Hospital, 25 had conservative and 30 had radical surgery, and their postoperative follow-up varied from 50 to 79 months. No patient was lost to follow-up. Among the 55 patients, 36 intended to get pregnant after surgery, 23 of whom had unsuccessfully attempted to conceive for more than 12 months before surgery (63%). At the end of follow-up, 29 patients achieved pregnancy (81%), and natural conception was recorded in 17 of them (59% of conceptions). As several women had more than 1 pregnancy (range: 0–3), we recorded 37 pregnancies, 24 natural conceptions (65%) and 29 deliveries (78%). The probabilities of achieving pregnancy at 12, 24, 36 and 48 months postoperatively were 33.4% (95% CI: 20.6–51.3%), 60.6% (44.8–76.8%), 77% (61.5–89.6%) and 86.8% (72.8–95.8%), respectively. Women who had been advised to attempt natural conception

achieved pregnancy significantly earlier than patients referred for ART ($P = 0.008$). In infertile patients, the postoperative pregnancy rate was 74%, and 53% of conceptions were natural.

LIMITATIONS, REASONS FOR CAUTION: The main outcomes of the original trial were related to digestive function and not to fertility. Several factors impacting fertility could not be revealed due to small sample size. The study included a high percentage of young women with an overall satisfactory prognosis for fertility, as patients' median age was 28 years. The inclusion of only large infiltrations of the rectum does not allow the extrapolation of conclusions to small nodules of <2 cm in length. Only one skilled gynecologic surgeon performed all the procedures.

WIDER IMPLICATIONS OF THE FINDINGS: First-line surgery can be considered in patients with deep endometriosis infiltrating the rectum and pregnancy intention. Patients receiving advice from experienced surgeons on conception modes were more likely to conceive faster after surgery.

STUDY FUNDING/COMPETING INTEREST(S): This work was supported by a grant from the clinical research program for hospitals (PHRC) in France. The authors declare no competing interests related to this study.

TRIAL REGISTRATION NUMBER: The original randomized trial is registered with ClinicalTrials.gov (number NCT 01291576).

Key words: endometriosis / infertility / pregnancy rate / postoperative / bowel / rectum / surgery / colorectal resection / disc excision / shaving

Introduction

Surgical management of deep infiltrating endometriosis (DIE) of the rectum has become a topic of increasing interest in gynecological surgery, leading to much debate. In women with pregnancy intention, optimal management such as surgery versus first-line ART for patients with severe endometriosis is strongly debated. The absence of randomized trials comparing primary surgery with first-line IVF allows limited interpretation of available studies, most of which were non-comparative, retrospective cohorts. Consequently, the ESHRE recently stated that there was no evidence supporting surgical management of deep endometriosis prior to ART to improve pregnancy rate (Dunselman et al., 2014). However, it was accepted that women planning pregnancy and suffering from pain may benefit from surgical management with favorable impact on painful complaints (Dunselman et al., 2014). Since ESHRE recommendations, several studies have suggested that the surgical removal of deep endometriosis nodules might have a favorable impact on IVF outcomes (Bianchi et al., 2009; Ballester et al., 2017; Bendifallah et al., 2017). In addition, the probability of postoperative spontaneous conception in patients undergoing complete resection of deep endometriosis was satisfactory in several series previously reported in the literature (Roman et al., 2015, 2018; Iversen et al., 2017; Cohen et al., 2014).

We recently reported the results of a randomized trial, the main goal of which was to compare digestive and urinary outcomes in 60 patients managed for deep endometriosis infiltrating the rectum by either conservative rectal surgery using shaving or disc excision, or by radical colorectal segmental resection (Roman et al., 2018). During the 24-month follow-up, 34 patients attempted pregnancy, 14 of whom (41%) conceived naturally, while another six conceptions (18%) were obtained with ART. Institutional review board approval was obtained to extend the follow-up period to 10 years for the 55 women enrolled at Rouen University Hospital, in order to assess long-term postoperative outcomes.

The aim of our study was to assess fertility outcomes in women with pregnancy intention and postoperative follow-up exceeding 4 years.

Materials and Methods

We conducted a postoperative survey in patients enrolled in the ENDORE randomized trial (ENDORE, NCT 01291576) (Roman et al., 2018). The trial was unblinded, 1:1 parallel-arms, controlled randomized, the main goal of which was to assess the hypothetical superiority of conservative rectal surgery over segmental resection in the management of deep endometriosis infiltrating the rectum. The study protocol was entirely reported in a recent work (Roman et al., 2018). Eligible patients were over 18 and under 45 years and managed for deep endometriosis infiltrating the rectum up to 15 cm from the anus, measuring more than 20 mm in length, involving at least the muscular layer in depth, and up to 50% of rectal circumference. When deep endometriosis respecting inclusion criteria was revealed (at least one imaging technique providing rectal infiltration over 2 cm in length), patients were proposed enrollment in the trial and explained the principles and the aim of the study. Assignment of a patient to conservative surgery or colorectal resection was based on randomization lists drawn up separately for each center by a statistician with no clinical involvement in the trial (M.B.). The details, like the block size, were not revealed to investigators before the end of the study. Instead, the investigator of each center received 60 sequentially numbered, opaque, sealed envelopes, which were opened only after the patient had completed all baseline assessments and had given written consent to be enrolled in the trial. To prevent subversion of the allocation sequence, the first two letters of the last name, the first letter of the first name and the date of birth were immediately faxed to the sponsor. Once the fax had been received, the patient could no longer be excluded from the trial. Between March 2011 and August 2013, patients were enrolled in three referral centers in France, i.e. Rouen University Hospital, Tenon University Hospital, and Lille University Hospital and followed up for 24 postoperative months. In patients enrolled at Rouen University Hospital, the local Internal Review Board gave approval to extend follow-up until 10 years.

Patients underwent randomization before surgery and were duly informed of the results of randomization. The surgical management of patients enrolled in the trial has been recently reported (Roman et al., 2018). One gynecologist experienced in deep endometriosis surgery performed all the procedures, assisted when required by three general surgeons experienced in colorectal surgery. Ovarian endometriomas were exclusively managed by ablation using plasma energy (Roman et al., 2015).

Fallopian tube patency was systematically checked intraoperatively, and hydrosalpinges were either removed or interrupted. On the basis of patients' characteristics (age, parity, antecedents of surgery, ovarian reserve), male sperm characteristics, intraoperative findings (endometriosis stage, involvement of ovaries and fallopian tubes, as well as the possibility of restoring them without harm) the surgeon postoperatively recommended either natural conception or ART management.

At baseline, patients filled in questionnaires including questions about pelvic complaints related to endometriosis using Visual Analog Scale (VAS), bowel movements and bladder voiding, as well as several standardized questionnaires assessing gastrointestinal and urinary function, and quality of life (Roman *et al.*, 2018). They were followed up at 6, 12, 18 and 24-month visits after surgery, then yearly until 10 years postoperatively. Digestive and urinary outcomes were assessed using the same questionnaires as at baseline. Fertility outcomes were recorded, including pregnancy intention, conception mode, pregnancy outcome, ART management and delivery mode. The event dates considered to analyze time-to conception were the date of surgery or the day when postoperative medical treatment was discontinued, and the day of conception or of last follow-up visit.

Statistical analysis was performed using Stata 11.0 software (Stata Corporation, Lakeway Drive, TX, USA). The population was described using median, first and third quartile (Q1–Q3) if the characteristics had at least ordinal level and were not categorized. Fisher's exact test was employed for categorical characteristics; otherwise, Wilcoxon's test was used for independent samples. Kaplan Meier and actuarial life-table analysis were used to estimate pregnancy likelihood as a function of follow-up with 95% CIs, and were compared using the log-rank test. Cox's model was used to identify independent predictive factors for pregnancy likelihood. $P < 0.05$ was considered statistically significant.

Results

Overall, 55 patients were enrolled and randomized at Rouen University Hospital. A total of 25 patients had conservative techniques and 30 patients had radical surgery (Roman *et al.*, 2018). Their postoperative follow-up varied from 50 to 79 months. No patient was lost to follow-up.

In total, 36 patients intended to get pregnant during follow-up (Video 1). Their baseline characteristics and intraoperative findings are presented in Tables I and II. Among them, 23 patients had unsuccessfully attempted to conceive before surgery for more than 12 months (63%). At the end of follow-up, 29 patients achieved pregnancy (81%) (Fig. 1). Among them, 17 conceived naturally (47% of women, 59% of conceptions), and 12 conceived using ART techniques (41% of conceptions): 10 patients had IVF, 1 patient had intrauterine insemination, and 1 patient received oocyte donation due to preoperative ovarian failure. In 10 of these 12 patients, ART management had been recommended immediately after surgery, without attempting natural conception, while in the remaining two patients ART was initiated after 9 months of unsuccessful attempts at natural conception. Primary ART management was required because of severe oligoastheno-zoospermia in two patients' partners, and because of polycystic ovary syndrome and fallopian tube obstruction in four women in each group, respectively. The median value of the number of IVF required to achieve pregnancy was 1 (range from 1 to 3).

In the group of 23 infertile patients, 17 women achieved pregnancy (74%) and 9 conceived naturally (39%).

Among the seven patients with conception failure, two patients had preoperative ovarian failure with preoperative AMH respectively at 0.2 and 0.3 ng/mL: the first patient was a 26-year nullipara and

Table I Patients' baseline characteristics.

Parameter	N = 36
Age (years)	28 (23–39)
Surgical antecedents related to endometriosis	9 (25)
BMI	23.9 (17.3–33.1)
Nulligesta	21 (58.3)
Nullipara	27 (75)
Unsuccessful pregnancy attempt for > 12 months	23 (63.9)
Previous infertility care	15 (41.7)
Dysmenorrhea	36 (100)
VAS of dysmenorrhea	9 (3–10)
Sexual intercourse during past year	36 (100)
Dyspareunia	31 (86.1)
VAS of dyspareunia	5 (1–8)
Chronic intermenstrual pelvic pain	26 (72.2)
VAS of intermenstrual chronic pelvic pain	5 (2–9)
Biberoglou and Behrman score	4 (2–7)
Digestive symptoms	
≤ 1 stool/5 days	11 (30.6)
Defecation pain	30 (83.3)
≥ 3 stools/day	13 (36.1)
Involuntary gas or stool loss	8 (22.2)
GIQLI score	93 (57–140)
KESS score	10 (0–26)
Wexner score	0 (0–7)
How long were you able to defer defecation?	
< 5 min	4 (11.1)
5–10 min	8 (22.2)
10–15 min	2 (5.6)
> 15 min	22 (61.1)
Urinary symptoms	
USP score	0 (0–5)
Short Form 36 Health Survey score	59.8 (17.3–88.5)
Localization of deep nodules of digestive tract	
- Rectal nodules	
1 nodule	34 (94.4)
2 nodules	2 (5.6)
- Sigmoid colon nodules	
1 nodule	12 (33.3)
2 nodules	2 (5.6)
3 nodules	1 (2.8)
- Left, transverse, right colon and cecum nodules	2 (5.6)
Diameter of largest rectal nodule (mm)	30 (20–60)
Deepest infiltration of the rectum	
- muscular layer	25 (69.4)
- submucosa	10 (27.8)
- mucosa	1 (2.8)
Height of the lowest nodule (mm from anal verge)	85 (30–150)

Data are *n* (%) or median (min–max). VAS, visual analog scale; GIQLI, gastrointestinal quality of life index; KESS, Knowles–Eccersley–Scott symptom; USP, urinary symptom profile.

Table II Intraoperative findings and surgical procedures.

Parameter	Patients (n = 36)
Randomization	
Conservative arm	16 (44.4)
Colorectal resection arm	20 (55.6)
Operative route	
Laparoscopic	32 (88.9)
Laparoscopic converted to open surgery	4 (11.1)
Operative time (min)	280 (120–650)
Procedure performed on the rectum	
Shaving	3 (8.3)
Full thickness disc excision	11 (30.6)
Colorectal segmental resection	22 (61.1)
Full thickness disc excision	
Diameter of the specimen (mm)	50 (30–70)
Height of rectal suture (mm)	70 (40–100)
Colorectal segmental resection	
Length of colorectal specimen (mm)	80 (20–200)
Height of colorectal anastomosis (mm)	80 (50–150)
Temporary stoma	28 (77.7)
Ileostoma	8 (22.2)
Colostoma	20 (56.6)
AFSr score	58 (10–150)
Ablation of ovarian endometrioma using plasma energy	16 (44.4)
Right ovary	11 (30.6)
Left ovary	12 (33.3)
Resection of bladder nodule	2 (5.6)
Management of ureteral endometriosis	6 (16.6)
Advanced ureterolysis	5 (13.9)
Resection of the ureter and reimplantation in the bladder	1 (2.8)
Segmental resection of sigmoid colon (separated from rectal procedure)	3 (8.3)
Selective resection of left, transverse, right colon or cecum	2 (5.6)
Appendectomy	5 (13.9)
Resection of posterior vagina	30 (83.3)
Omentoplasty	30 (83.3)
Intraoperative blood loss (mL)	200 (100–800)
Blood transfusion	0

Data are n (%) or median (Q1–Q3). AFSr, revised American Fertility Society score.

underwent two unsuccessful postoperative IVF, and the second patient was 36 years old who refused ART. In a 30-year nullipara, postoperative AMH dropped from 3.5 to 0.3 ng/mL, despite the absence of ovarian endometrioma and no surgical procedure on the ovaries; since surgery, this patient has declined ART management, and has unsuccessfully attempted natural conception for 60 months. Two nulliparas (23 and 25 years old) with normal ovarian reserve are currently undergoing ART management, however no pregnancy has

resulted after respectively two and three IVF procedures, respectively. One 27-year-old patient with normal ovarian reserve has unsuccessfully attempted natural conception and is scheduled for IVF. One 27-year-old patient has temporarily and unsuccessfully attempted natural conception for 6 months, with no intention for ART management.

During the whole follow-up period, patients achieved up to three postoperative pregnancies. We recorded a total of 37 pregnancies, among which 24 were natural (65%), and 29 deliveries of healthy babies (78%).

The probability of achieving pregnancy at 12, 24, 36 and 48 months postoperatively were 33.4% (95% CI: 20.6–51.3%), 60.6% (44.8–76.8%), 77% (61.5–89.6%) and 86.8% (72.8–95.8%), respectively (Fig. 2). Women who had been advised to attempt natural conception achieved pregnancy significantly earlier than patients referred for ART ($P = 0.008$) (Fig. 3). Figure 4 presents a Kaplan Meier curve of the probability of pregnancy after the discontinuation of postoperative medical treatment, showing that a large majority of patients conceived naturally during a period of 12 months. Patients advised to attempt natural conception by experienced surgeons on the basis of pre- and intraoperative criteria above mentioned were more likely to conceive after the arrest of medical treatment than those directed to ART ($P = 0.004$). Preoperative infertility did not significantly impact the probability of conceiving after removal of deep endometriosis nodules (Table III).

A total of 28 patients had diverting stoma for a period varying from 3 to 4 months, except for two patients with rectovaginal fistula in whom the reversal was carried out 6 and 20 months postoperatively, respectively. All the patients had continuous medical treatment until the stoma was closed, thus the interval before stoma closure was not suitable for conception. This time delay was not taken into account to calculate the probability of conception after the discontinuation of postoperative medical treatment (Fig. 4).

Discussion

Our study reveals that skilled surgical management for symptomatic large deep endometriosis nodules infiltrating the rectum in young women is followed by a high pregnancy rate 4 years after surgery. Although a majority of patients had a past history of infertility, most pregnancies resulted from postoperative natural conception. Patients receiving advice from experienced surgeons to attempt natural conception were more likely to conceive faster after the surgery. Our data suggest that experienced surgical teams may safely offer surgical management of endometriosis for patients with deep endometriosis and pregnancy intention, with very good fertility outcomes.

Our study has several limitations. Patients were originally enrolled in a randomized trial the main outcome of which was related to postoperative digestive and urinary function. Consequently, the sample size was small and did not concern all patients managed for deep endometriosis of the rectum in our department. Fertility outcomes were secondary endpoints, and the choice of conception mode after surgery was not determined by our study design. Pre- and postoperative fertility assessment was not uniformly performed or available. The sample size was small for a meaningful comparison between conservative and radical colorectal surgery, in terms of postoperative fertility. The inclusion of only large infiltrations of the rectum does not allow the extrapolation of conclusions to small nodules of <2 cm in length. However, we chose to include only large nodules due to the presumption that many surgeons would consider segmental resection

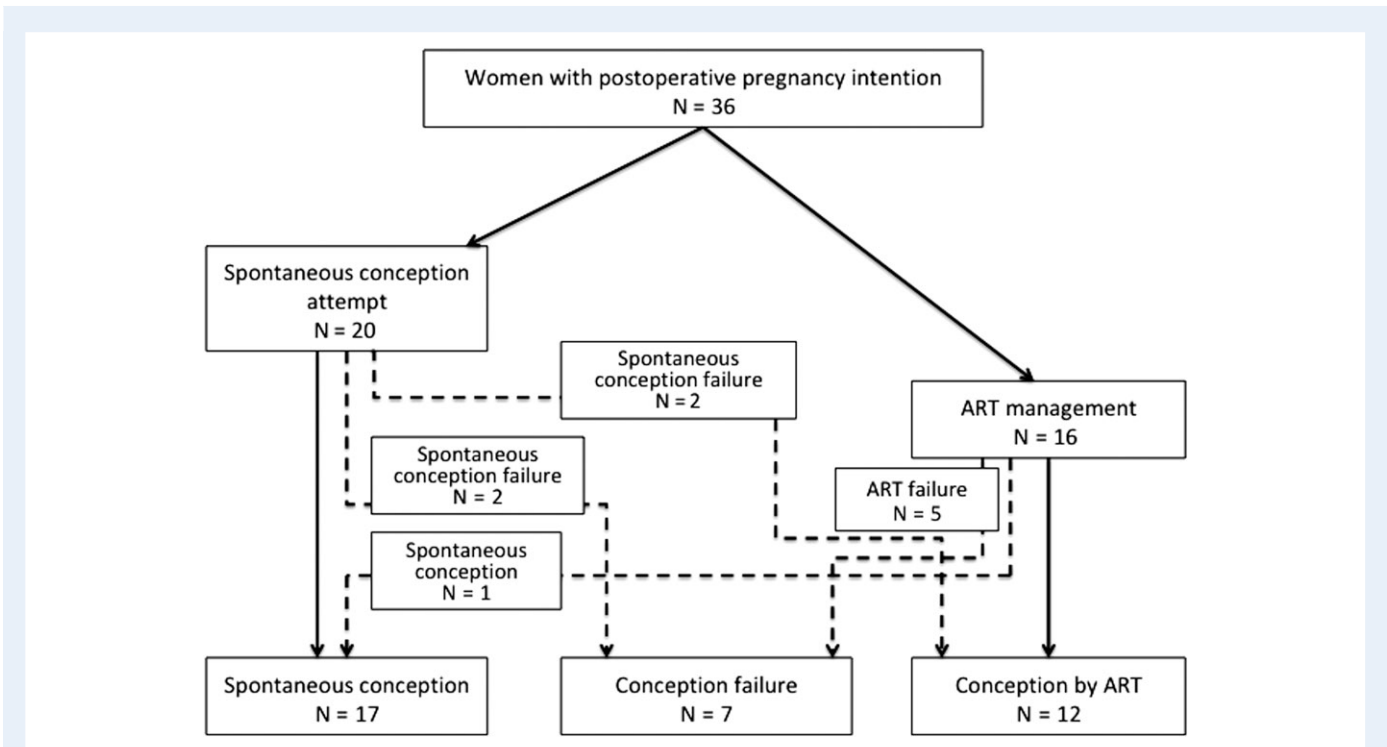


Figure 1 Study flow chart.

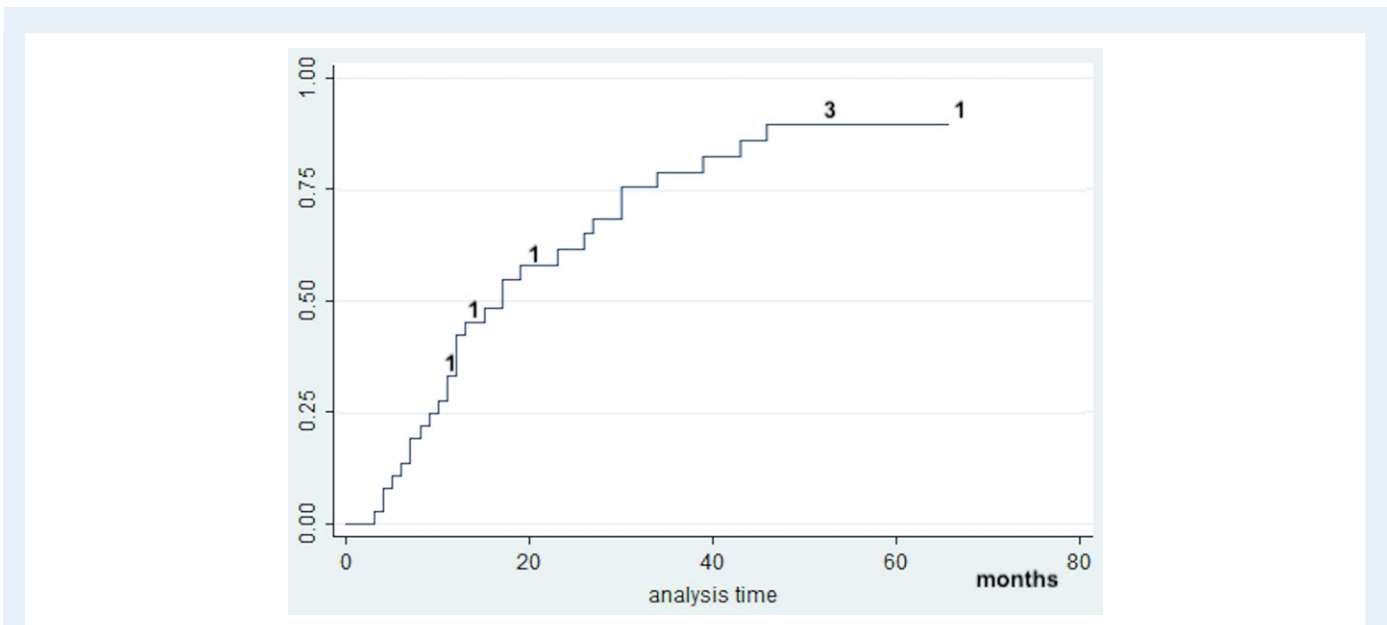


Figure 2 Kaplan–Meier curves presenting the probability (y-axis) of postoperative pregnancy. The x-axis represents the number of postoperative months. Numbers on the curve represent right censored data; before 50 weeks these are women who ceased trying to conceive at this time (but completed follow-up).

to be an overtreatment in small rectal nodules. All the procedure were performed in an expert center by a gynaecologist experienced in the management of deep endometriosis, using an original technique to treat ovarian endometriomas (Roman et al., 2015b), thus the results might not automatically be reproducible.

Nevertheless, our study has several strengths. Patients were managed exclusively by an experienced surgeon, particularly concerned by the conservation of patients’ ability to conceive after surgery. Since the trial was prospective, the patients were carefully followed up and assessed, allowing for accurate long-term results. Last but not least,

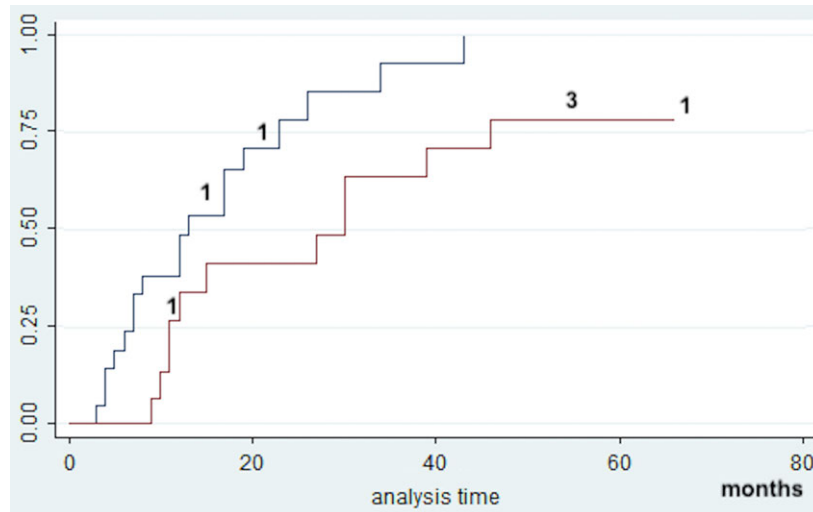


Figure 3 Kaplan–Meier curves presenting the probability (y -axis) of postoperative pregnancy according to the conception mode recommended at the end of surgery (natural conception—blue line; ART management—red line). The x -axis represents months since the operation. Numbers on the curve represent right censored data; before 50 weeks these are women who ceased trying to conceive at this time (but completed follow-up). Women who had been advised to attempt natural conception achieved pregnancy significantly earlier than patients referred for ART ($P = 0.008$).

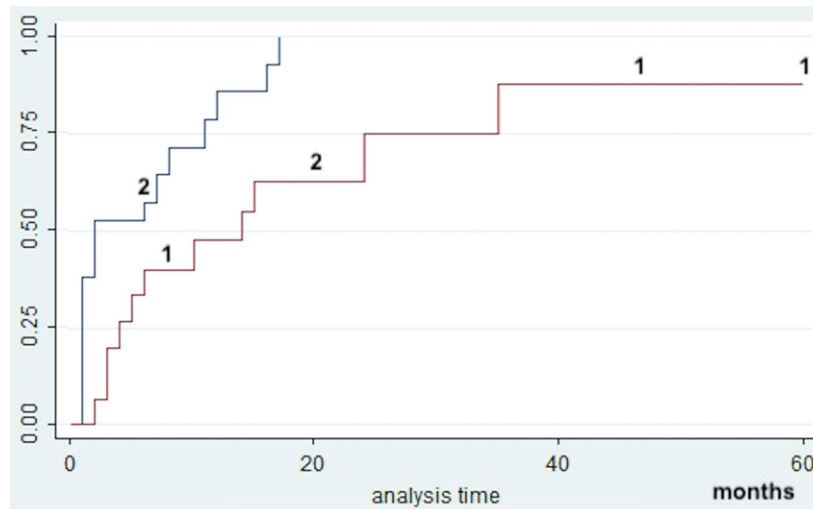


Figure 4 Kaplan–Meier curves presenting the probability (y -axis) of postoperative pregnancy according to the conception mode recommended at the end of surgery (natural conception—blue line; ART management—red line). The x -axis represents months since postoperative medical treatment was stopped. Numbers on the curve represent right censored data; before 50 weeks these are women who ceased trying to conceive at this time (but completed follow-up). Women who had been advised to attempt natural conception achieved pregnancy significantly earlier than patients referred for ART ($P = 0.004$).

our data focus on postoperative pregnancy rate, which is a question of major interest in the dynamic topic of the management of deep endometriosis.

Although 63% of patients had unsuccessfully attempted to conceive before surgery, natural conception occurred after surgery in 47% of them. This result suggests that surgical management enables natural conception in women with deep endometriosis of the rectum, for

whom the likelihood of preoperative conception was not found to vary over 13% (Vercellini et al., 2006; Roman, 2015). Furthermore, fertility may have been restored by surgery, hence, preoperative infertility no longer significantly impacted postoperative conception.

When compared with previous reports in the literature, the pregnancy rates observed in our study are encouraging. Several studies have focused on postoperative fertility outcomes in women managed

Table III Independent predictive factors of postoperative fertility (Cox's model).

Risk factor	N	Pregnancy	HR	HR 95% CI	P
Pregnancy rate from the day of surgery					
Age					0.59
<35 years	30	24	1		
≥35 years	6	5	1.4	0.43–4.4	
Unsuccessful pregnancy attempt for >12 months					0.80
No	13	12	1		
Yes	23	17	1.1	0.46–2.7	
Surgical procedure					0.40
Conservative surgery	16	13	1		
Colorectal resection	20	16	0.71	0.33–1.6	
Surgeon's advice to conceive					0.02
Spontaneously	21	18	1		
ART	15	11	0.35	0.14–0.85	

for colorectal endometriosis. In a recent review (Cohen *et al.*, 2014) of series of patients presenting with bowel involvement, exclusively managed by colorectal resection ($n = 1320$), the postoperative rates of natural conception and overall conception were 28.6% (95% CI: 25–32.3) and 46.9% (95% CI: 42.9–50.9), respectively. In a prospective trial (Meuleman *et al.*, 2014) conducted in patients having undergone colorectal resection for deep endometriosis, the postoperative rates of natural conception, overall conception and ART induced conception were 24% (13/54), 50% (27/54) and 26% (14/54). In our database, 65% of patients operated for associated colorectal endometriosis and ovarian endometriomas conceived after surgery and 60% of these pregnancies were natural (Roman *et al.*, 2015). We previously estimated that ~74.5% of pregnancies occurred during the first 3 years after surgery (Roman *et al.*, 2015).

These results should be compared with pregnancy rates reported in series including women with colorectal endometriosis and pregnancy intention, who were managed by first-line IVF. Primary IVF is often recommended instead of surgery, specifically to shorten the delay in conception and to prevent the risk of postoperative ovarian reserve impairment, and the negative impact of potential postoperative complications. In a multicenter study enrolling 75 patients with colorectal endometriosis, the cumulative pregnancy rate (CPR) after three cycles of ICSI-IVF was estimated at 68.6% (95% CI: 40–83.6%) (Ballester *et al.*, 2012). The estimation was higher for women with normal AMH values (62.7% of cases) and without adenomyosis (prevalence at 28%). In this series, 68% of women had ovarian endometriomas. Despite high CPR values, only 32 patients actually conceived during follow-up (42.7%) (Ballester *et al.*, 2012). Another study found that for ICSI-IVF, the pregnancy rate of patients with colorectal DIE involving the rectum was comparable to that of patients with tubal or male infertility (Mathieu d'Argent *et al.*, 2010). In 29 patients with colorectal DIE, the authors recorded 29 starting cycles, 24 embryo transfer (83%), 12 pregnancies (41%) and 8 deliveries.

It is noteworthy that 37% of our patients were not known to be infertile before surgery. Indeed, either they had not tried to conceive before surgery or they had been trying for <12 months, thus they did

not fulfill criteria for infertility. Surgery was routinely performed in all patients referred to our department with both pain and pregnancy intention. Young patients such as these, when referred to other facilities which prefer first-line IVF, receive ART management and are thus automatically recorded as 'infertile'. It is therefore highly likely that the rates of 'infertile' women are underestimated in series of patients managed by primary surgery when compared with those undergoing primary ART. In our opinion, the baseline characteristics of our patients are comparable to those reported in studies such as those of Ballester *et al.* (2012) or Mathieu d'Argent (2010).

It may be easier for many women with severe DIE to initially undergo IVF due to a higher number of IVF centers versus multidisciplinary endometriosis centers as well as full reimbursement of IVF cycles in several countries. Primary IVF is often proposed instead of surgery, specifically to shorten the delay in conception and to prevent the risk of postoperative ovarian reserve impairment and the negative impact of potential postoperative complications on patient fertility. The risk of postoperative ovarian failure should be considered, as in our series we observed one patient free of ovarian endometriomas who presented an unexpected drop in postoperative AMH. The risk of severe complications following surgery for DIE can be perceived as unpredictable or inevitable, although the frequency and long-term impact on fertility is limited. For experienced surgical teams, the risk of complications is lower and the frequency of rectovaginal fistulae is close to 3%, but repaired without sequelae in the majority of cases (Roman *et al.*, 2017, 2018). Deep pelvic abscesses occur in fewer than 5% of cases and can be drained without long-term consequences. Surgery for DIE can be performed laparoscopically in more than 90% of cases, considerably reducing the risk of adhesions, postoperative pain, duration of convalescence, and allows spontaneous conception (Roman *et al.*, 2017, 2018). However, the rate of postoperative complications reported by experienced surgical teams may be lower than that reported by surgeons with low volume of activity (Bendifallah *et al.*, 2018), hence these results may not apply in all settings. The risk of major postoperative complications may worry some patients or physicians, who consequently could prefer first-line IVF instead of colorectal surgery. Despite the general presumption that ART allows shorter delays to conceive, our study demonstrates that patients advised to conceive naturally after surgery conceived faster than those referred for ART.

However, caution should be taken before concluding that surgical management should be recommended as first-line treatment for infertility in women with colorectal endometriosis. The effect of surgery for colorectal endometriosis as a fertility-enhancing procedure is defined based primarily on natural conception. Ideally, the best design to quantify the effect size of this type of surgery is randomization to surgery (experimental arm) versus expectant management (control arm), considering natural conception rate as the main study objective. With this design, the incremental benefit of surgery over the background probability of conception could be quantified. In fact, women and surgeons cannot reliably know the anatomic conditions of fallopian tubes and ovaries before surgery. Indeed, in daily practice the decision to perform surgery is taken without reliable knowledge of the anatomic conditions of the fallopian tubes and ovaries. As the mode of conception in our study was determined after surgical exploration of the pelvic organs, these results regarding mode of conception cannot necessarily be applied to a non-surgical population.

On the other hand, the number of women who achieved pregnancy by IVF was too small to draw any meaningful conclusions about the impact of the surgery on IVF outcomes. The original trial randomized the patients on the basis of the surgical technique performed on the rectum, and not on the conception mode or whether colorectal surgery was performed before IVF or not. More consistent data may be provided by a randomized trial assessing the impact of colorectal surgery on IVF performance, which is on going in several French facilities including ours (Collinet, 2017).

Deep endometriosis is known to be related to infertility and is often the cause of severe dyspareunia, which may impede regular sexual intercourse necessary for natural conception. Many patients diagnosed with such a disease are convinced that the only mode of conception is to undergo ART and to keep their painful nodule, and to postpone or never have surgery. Our study shows that both surgery and pregnancy are very often possible. It also highlights the advisory role of the surgeon regarding the likelihood of natural conception and pregnancy after surgery and whether ART really is necessary. Physicians should ultimately offer patients a balanced perspective of the potential benefits and potential harms of alternative options, including considerations on the strength of the available evidence supporting them, in order to help them in choosing the best strategy adapted to their goals, symptoms and beliefs.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

The authors are grateful to Amélie Bréant for the management of data, and to Nikki Sabourin-Gibbs, Rouen University Hospital, for her help in editing the article.

Authors' roles

H.R. designed the trial, performed the surgery, wrote the first draft of the article. M.F. and S.T. performed statistical analysis. B.M. and I.C.L. performed data collection. M.B. and S.B. reviewed the article. All authors contributed to the final version of the article.

Funding

This work was supported by a grant from the clinical research program for hospitals (PHRC) in France.

Conflict of interest

The authors declare no conflict of interest related to this study.

Competing interest(s)

The authors declare no competing interests related to this study.

References

- Ballester M, Mathieu d'Argent E, Morcel K, Belaisch-Allart J, Nisolle M, Dara E. Cumulative pregnancy rate after ICSI-IVF in patients with colorectal endometriosis: results of a multicentre study. *Hum Reprod* 2012; **27**:1043–1049.
- Ballester M, Roman H, Mathieu E, Touleimat S, Belghiti J, Darai E. Prior colorectal surgery for endometriosis-associated infertility improves ICSI-IVF outcomes: results from two expert centres. *Eur J Obstet Gynecol Reprod Biol* 2017; **209**:95–99.
- Bendifallah S, Roman H, Mathieu d'Argent E, Touleimat S, Cohen J, Darai E, Ballester M. Colorectal endometriosis-associated infertility: should surgery precede ART? *Fertil Steril* 2017; **108**:525–531.e4. In press.
- Bendifallah S, Roman H, Rubod C, Leguevaque P, Watrelot A, Bourdel N, Ballester M, Darai E. Impact of hospital and surgeon case volume on morbidity in colorectal endometriosis management: a plea to define criteria for expert centers. *Surg Endosc* 2018; **32**:2003–2011.
- Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL, Serafini PC. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009; **16**:174–180.
- Cohen J, Thomassin A, Mathieu d'Argent E, Laas E, Canlorbe G, Zilberman S, Belghiti J, Thomassin-Naggara I, Bazot M, Ballester M et al. Fertility before and after surgery for deep infiltrating endometriosis with and without bowel involvement: a literature review. *Minerva Ginecol* 2014; **66**:575–587.
- Collinet P. *Impact of Complete Surgery of Colorectal Deep Infiltrating Endometriosis on Fertility (ENDOFERT) NCT02948972*. <https://www.clinicaltrials.gov/ct2/show/NCT02948972?term=Collinet&cond=Endometriosis&cntry=FR&city=Lille&rank=1>. (6 April 2018, date last accessed).
- Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Home AW, Kiesel L, Nap A et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014; **29**:400–412.
- Iversen ML, Seyer-Hansen M, Forman A. Does surgery for deep infiltrating bowel endometriosis improve fertility? A systematic review. *Acta Obstet Gynecol Scand* 2017; **96**:688–693.
- Mathieu d'Argent E, Coutant C, Ballester M, Dessolle L, Bazot M, Antoine JM, Darai E. Results of first in vitro fertilization cycle in women with colorectal endometriosis compared with those with tubal or male factor infertility. *Fertil Steril* 2010; **94**:2441–2443.
- Meuleman C, Tomassetti C, Wolthuis A, Van Cleynenbreugel B, Laenen A, Penninckx F, Vergote I, D'Hoore A, D'Hooghe T. Clinical outcome after radical excision of moderate-severe endometriosis with or without bowel resection and reanastomosis. A prospective cohort study. *Ann Surg* 2014; **259**:522–531.
- Roman H. Colorectal endometriosis and pregnancy wish: why doing primary surgery. *Front Biosci (Schol Ed)* 2015; **7**:83–93.
- Roman H, FRIENDS group (French coloRectal Infiltrating ENDometriosis Study group). A national snapshot of the surgical management of deep infiltrating endometriosis of the rectum and colon in France in 2015: a multicenter series of 1135 cases. *J Gynecol Obstet Hum Reprod* 2017; **46**:159–165.
- Roman H, Bubenheim M, Huet E, Bridoux V, Zacharopoulou C, Darai E, Collinet P, Tuech JJ. Conservative surgery versus colorectal resection in deep endometriosis infiltrating the rectum: a randomized trial. *Hum Reprod* 2018; **33**:47–57.
- Roman H, Quibel S, Auber M, Muszynski H, Huet E, Marpeau L, Tuech JJ. Recurrences and fertility after endometrioma ablation in women with and without colorectal endometriosis: a prospective cohort study. *Hum Reprod* 2015; **30**:558–568.
- Vercellini P, Pietropaolo G, De Giorgi O, Daguati R, Pasin R, Crosignani PG. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile? *Am J Obstet Gynecol* 2006; **195**:1303–1310.