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## Nomogram predicting the likelihood of live-birth rate after surgery for deep infiltrating endometriosis without bowel involvement in women who wish to conceive: A retrospective study



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### ABSTRACT

**Objective:** To study the fertility and live birth (LB) rate in women after surgery for deep infiltrating endometriosis (DIE) without bowel involvement and to evaluate the predictive factors of LB after DIE surgery without bowel involvement.

**Study design:** Retrospective cohort study. A total of 118 women who wished to conceive and who underwent surgery for DIE without bowel involvement were analyzed between January 2006 and December 2014. A multivariate logistic regression analysis of selected factors and a nomogram to predict the subsequent LB rate was constructed.

**Results:** Thirty-six women had a LB (30.5%). In multivariate analysis, factors associated with a LB were: age  $\leq 30$  years ( $p=0.0024$ ), BMI  $\leq 25$  kg/m<sup>2</sup> ( $p=0.029$ ) and Enzian grade 1 ( $p<0.001$ ). These factors were associated to develop a nomogram. Before and after the bootstrap sampling procedure, the predictive model had an AUC of 0.84 (95% CI, 0.82–0.86) and 0.81 (95% CI, 0.79–83), respectively, and showed a good calibration.

**Conclusions:** This work presents the originality of describing the fertility and the LB rate after surgery for DIE without bowel involvement with a predictive model. Such tools can help clinicians to support the patient in making an informed decision about fertility treatment options, contributing to the decision-making process by defining simple risk factors of poor LB probability that can help identify good candidates for MAR.

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### Introduction

Deep infiltrative endometriosis (DIE) is a common gynecological pathology that affects up to 50% of infertile women [1].

While the association between DIE without bowel involvement and infertility is well supported throughout the literature, an absolute cause-effect relation has not been established [2]. Despite the publication of international guidelines, the management of endometriosis without bowel involvement and associated infertility remain unclear [3–10].

To date, although several scoring systems and nomograms have been published to evaluate the PR after ICSI-IVF in infertile patients [11–13], none of them: are applicable to patients with DIE without bowel involvement and were specifically developed to determine the individual live birth probability.

The objective of this study was therefore to develop a nomogram for the likelihood of live-birth rate (LBR) after surgery in women with DIE without bowel involvement and who wish to conceive, and establishing an optimal threshold to optimize post-surgical decision-making.

### Materials and methods

We conducted a retrospective analysis of our database using information from women with DIE without bowel involvement who wished to conceive and who underwent surgery from January

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2006 to December 2014 at Tenon University Hospital in Paris, France.

For each woman, the following parameters were recorded: age at surgery, body mass index (BMI), smoking status, presence of endometrioma and/or adenomyosis on magnetic resonance imaging (MRI), serum level of anti-Müllerian hormone (AMH), fertility before surgery, symptoms, previous surgery for endometriosis, type of surgery, surgical route, Enzian and ASRM scores calculated during surgery, occurrence of pregnancy (spontaneous or after medically assisted reproduction (MAR)) and obstetrical issues.

Patients were excluded if colorectal endometriosis was diagnosed pre-operatively during clinical examination and/or on imaging exams (MRI, pelvis ultrasound . . .).

Endometriosis surgery was performed by endoscopy. The first step of the surgery consisted in exploring the abdomino-pelvic cavity to exhaustively assess the endometriotic lesions and calculate the ASRM and Enzian scores. The endometrioma were treated by cystectomy when greater than 5 cm. The ureters were systematically identified before dissection and some degree of ureterolysis, either uni- or bilateral, was performed. Once the external lateral surface of the utero-sacral ligament had been fully liberated, the rectovaginal space and the homolateral pararectal fossa were opened. The utero-sacral ligaments and/or torus were removed if infiltrated. If the vaginal wall was involved, an en bloc resection including the utero-sacral ligaments and a partial colectomy was performed.

All patients underwent a first postoperative visit 4–6 weeks after surgery then once a year to evaluate fertility and obstetrical issues.

A nomogram was developed for the LBR in women who wished to conceive after surgery for DIE without bowel involvement. A multivariate analysis was performed using the logistic regression model and including all the factors that were statistically significant on univariate analysis or clinically relevant from the literature [8]. Missing values in the predictors were multiply imputed with chained equations (MICE) [9,10] before statistical analyses. The complexity of the model was controlled using the Akaike information criterion [11]. A P-value of 0.05 was considered significant. The final model equation was then organized as a nomogram designed to calculate patient-specific probabilities of a live birth after surgery. Values for each of the model covariates were mapped to points on a scale ranging from 0 to 100, with total points obtained for each model covariate mapped to the probability of a live birth associated with the area under the receiver-operating characteristic curve (AUC) to measure the model's discriminatory power. It is generally accepted that an AUC of 1.0 indicates perfect accuracy between cases with or without a live birth, an AUC of 0.7–0.8 indicates satisfactory discrimination, values of 0.8 represent good discrimination whereas an AUC of 0.5 indicates no relationship [12]. Calibration was assessed using plots that overlap the prediction model.

A bootstrapping technique to obtain relatively unbiased estimates (200 repetitions) was used for internal validation. The bootstrapping method is based on resampling obtained by randomly drawing data and replacing them with samples from the original dataset. It provides an estimate of the average optimism of the AUC of the receiver-operating characteristics (AUC-ROC) [13]. Calibration was assessed using plots that overlapped the prediction model.

The optimal threshold (cut-off probability) of the nomogram in terms of clinical utility defined by the Youden Index [14], was evaluated according to the ROC curve. The sensitivity, specificity, negative predictive values (NPVs), and positive predictive values (PPVs), were estimated at this threshold.

The categorical and numerical variables were analyzed using the  $\chi^2$  test and the Student t test, respectively. Differences were

considered significant at a P-value of 0.05. All analyses were performed using the R package with the Design, Hmisc, Design, Presence/absence (<http://lib.stat.cmu.edu/R/CRAN>).

Prospective recording of data was approved by the French authority CCTIRS (Advisory Committee on Information Processing in Healthcare Research) CEROG 2012-GYN-10-03. All the women gave their informed consent.

## Results

During the study period, 118 women with DIE without bowel involvement who wished to conceive underwent a resection of DIE. Epidemiological and surgical characteristics of the population are summarized in Table 1. The median age of the women was 30 years (range 19–45) and 100 (84.7%) were under 30. The median age was lower in the group of patients who conceived but there were no other epidemiological differences or differences in the surgical location of DIE (Table 1). Resection of DIE was performed by laparoscopy, without laparoconversion, for all the patients. In addition to the resection of the torus (corresponding to the posterior region of the uterine cervix where the uterosacral ligaments meet, at the upper half of the posterior surface of the cervix) and utero-sacral ligaments, 36 patients (30.6%) required a cystectomy for endometrioma and 24 patients a colectomy (20.3%).

No difference in the ASRM score was noted between patients who conceived and those who did not (median total score: 37 versus 30, respectively ( $p=0.38$ )). The rate of patients with ASRM stage I/II and III/IV in the group of patients who conceived and those who did not were 36.1% and 35.4%, and 63.9% and 64.6%, respectively (not significant). No difference in the proportion of patients with endometriomas who required a colectomy was noted between the groups. There were more patients with a grade 1 Enzian score in the group of patients who conceived.

Overall, the median time to conception after surgery was 6 months (range; 2–48) for spontaneous pregnancies and 19 months (4–48) for pregnancies following MAR. The overall PR was 39% (46/118). No stillbirths were reported. Sixteen patients (34.8%) became pregnant after MAR leading to 13 live births. Nine women had a miscarriage (six after spontaneous pregnancy and three after MAR). One woman who conceived spontaneously had an ectopic pregnancy.

The overall LBR was 30.5% (36/118): 47% (17/36) of live births occurred in the spontaneous pregnancy group and 53% (19/36) in the MAR group.

A BMI > 30 kg/m<sup>2</sup> ( $p=0.017$ ), and an AMH serum level >2 ng/ml ( $p=0.0006$ ) were predictive factors for obtaining a spontaneous pregnancy compared to a MAR pregnancy (Table 2). PRs at 12 and 24 months were similar in both groups (no statistically significant difference).

In multivariate analysis, age at diagnosis, BMI and Enzian score were significantly associated with the likelihood of live birth after surgery in infertile women who had undergone surgery (Fig. 1). These factors were included in the logistic regression model (Table 3). Although the AMH level was not statistically significantly associated with live birth, it was included in the construction of the predictive model due to its clinical relevance [8,15,16]. The predictive model had an AUC of 0.84 (95% CI, 0.82–0.86) before the 200 repetitions of bootstrap sample corrections and 0.81 (95% CI, 0.79–83) afterwards (Fig. 2A).

No difference was observed between the predicted probability obtained from the bootstrap correction and the actual probabilities of live birth ( $p=0.3829$ ) implying that the nomogram was well calibrated. The average difference and the maximal difference in predicted and calibrated probabilities of recurrence were 6.4% and 1.07%, respectively (Fig. 2B).

**Table 1**  
Characteristics of the overall population.

	Overall population n=118 n (%)	Women with no live births n = 82 n (%)	Women with live births n = 36 n (%)	P-Value <sup>b</sup>
<b>Mean age at diagnosis (range):</b>		30.8 (22–42)	28.6 (19–40)	
<b>Age ≤ 30 years:</b>				
- Yes	63 (53.4)	38 (46.3)	25 (69.4)	
- No	55 (46.6)	44 (53.7)	11 (30.6)	0.02
<b>BMI ≥ 25 kg/m<sup>2</sup>:</b>				
- Yes	19 (16.1)	16 (19.5)	3 (8.3)	
- No	89 (75.4)	60 (73.1)	29 (80.5)	
- NA <sup>a</sup>	10 (8.5)	6 (7.4)	4 (11.1)	0.15
<b>Smoking</b>				
- Yes	32 (27)	19 (23.2)	13 (36.1)	
- No	66 (56)	50 (61)	16 (44.4)	
- NA	20 (17)	13 (15.8)	7 (19.4)	0.09
<b>Infertility prior surgery</b>				
- Yes	66 (56)	47 (57.3)	19 (52.8)	
- No	52 (44)	35 (42.7)	17 (47.2)	0.65
<b>Prior surgery for endometriosis</b>				
- Yes	26 (22)	17 (20.7)	9 (25)	
- No	92 (78)	65 (79.3)	27 (75)	0.61
<b>MRI: adenomyosis</b>				
- Yes	17 (14.4)	10 (12.2)	7 (19.4)	
- No	99 (83.9)	72 (87.8)	27 (75)	
- NA	2 (1.7)	0 (0)	2 (5.6)	0.25
<b>Enzian score</b>				
- Grade 1	46 (39)	21 (25.6)	25 (69.5)	
- Grade 2	27 (22.9)	19 (23.2)	8 (22.2)	
- Grade 3	45 (38.1)	42 (51.2)	3 (8.3)	<0.0001
<b>ASRM score</b>				
- I/II	42 (35.6)	29 (35.4)	13 (36.1)	0.94
- III/IV	76 (64.4)	53 (64.6)	23 (63.9)	
- median	/	37	30	0.39
<b>Surgical route</b>				
- Laparoscopy	118 (100)	82 (100)	36 (100)	1
<b>Surgery resection: torus and/or utero-sacral ligaments</b>				
- Yes	82 (69.5)	60 (73.2)	22 (61.1)	
- No	36 (30.5)	22 (26.8)	14 (38.9)	0.19
<b>Surgery resection: torus and/or utero-sacral ligaments and cystectomy</b>				
- Yes	36 (30.5)	22 (26.8)	14 (38.9)	
- No	82 (69.5)	60 (73.2)	22 (61.1)	0.19

BMI: body mass index; AMH: antimullerian hormone; ASRM: american society for reproductive medicine.

<sup>a</sup> NA, not available.

<sup>b</sup> Univariate analysis.

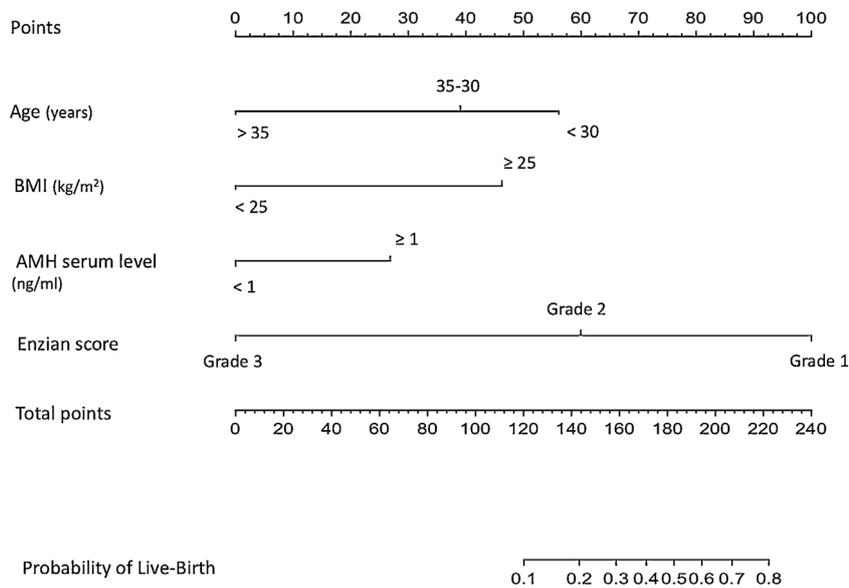
**Table 2**  
Characteristics of the population according to the type of pregnancy.

	Spontaneous pregnancy n= 31 n (%)	MAR pregnancy n= 16 n (%)	p value
<b>Age (year): ≤30</b>			
median, range	30 (19–41)	28.5 (22–38)	0.86
- Yes	22 (71)	10 (62.5)	0.55
- No	9 (29)	6 (37.5)	
<b>BMI (kg/m<sup>2</sup>) &gt;30</b>			
median, range	22 (17–29)	21 (16–30)	0.44
- Yes	0 (0)	3 (18.8)	0.04
- No	27 (87.1)	12 (75)	
- NA	4 (12.9)	1 (6.2)	
<b>Tobacco</b>			
- Yes	8 (25.8)	6 (37.5)	0.28
- No	19 (61.3)	6 (37.5)	
- NA	4 (12.9)	4 (25)	
<b>Prior surgery for endometriosis</b>	7 (22.6)	6 (37.5)	0.28
<b>AMH (ng/ml)</b>			
median, range	3.6 (1–6.1)	3.1 (0.48–6.7)	0.08
- <2	1 (3.2)	6 (37.5)	0.0004
- <1	0 (0)	2 (12.5)	0.03
- NA	12	7	
<b>MRI : adenomyosis</b>	5 (16.1)	4 (25)	0.46
<b>rASRM total score:</b>			
median, range	20 (4–124)	50 (4–114)	0.52
- Stade I, II	12 (38.7)	5 (31.2)	0.61
- Stade III, IV	19 (61.3)	11(68.8)	0.61
<b>ENZIAN score</b>			
- Grade 1	24 (77.4)	9 (56.2)	0.07
- Grade 2	6 (19.4)	3 (18.8)	
- Grade 3	1 (3.2)	4 (25)	
<b>Surgery resection: torus and/or utero-sacral ligaments</b>	22 (71)	8 (50)	0.09
<b>Pregnancy rate at 12 months</b>	24 (77.4)	9 (56.3)	0.18
<b>Pregnancy rate at 24 months</b>	29 (93.5)	12 (75)	0.25

The optimal threshold in terms of statistical and clinical utility was defined by a 20% Youden index [20]. At this threshold, sensitivity, specificity, positive predictive and negative predictive values of the model were 70.7%, 86.1% 92.1%, and 56.4%, respectively.

Applying this threshold, a subset of women of poor prognosis (i.e., the subgroup of women with a low likelihood of obtaining a live birth after surgery) was defined as those with a predicted probability of live birth under 20%. In this subset, the PR and LBR were 14.2% (9/63) and 7.9% (5/63), respectively. Above the 20% threshold, the likelihood of obtaining a live birth after surgery was high with a PR and LBR at 70.9% (39/55) and 56.4% (31/55), respectively. Fig. 3 highlights the cumulative LBR according to the optimal threshold ( $p < 0.001$ ) for the whole population.

For women with a Youden index under 20% who conceived spontaneously, the PR and LBR were 3.4% (2/58) and 1.7% (1/58), respectively. Above the 20% threshold, the PR and LBR were 63.6% (28/44) and 50.0% (22/44), respectively. Fig. 4 highlights the cumulative LBR according to the optimal threshold ( $p < 0.001$ ) for women who conceived spontaneously.



**Fig. 1.** The probability of a live birth is calculated by drawing a line to the point on the axis for each of the following variables: age, BMI, AMH and Enzian score. The points for each variable are summed and located on the total points line. Next, a vertical line is projected from the total points line to the predicted probability bottom scale to obtain the individual probability of a live birth.

## Comments

To the best of our knowledge, the nomogram we present here is the first to evaluate the individual likelihood of a live birth after surgery for DIE without bowel involvement in women who wish to conceive. Its clinical interest lies in the inclusion of readily available clinical, biological and surgical characteristics which are commonly used in practice.

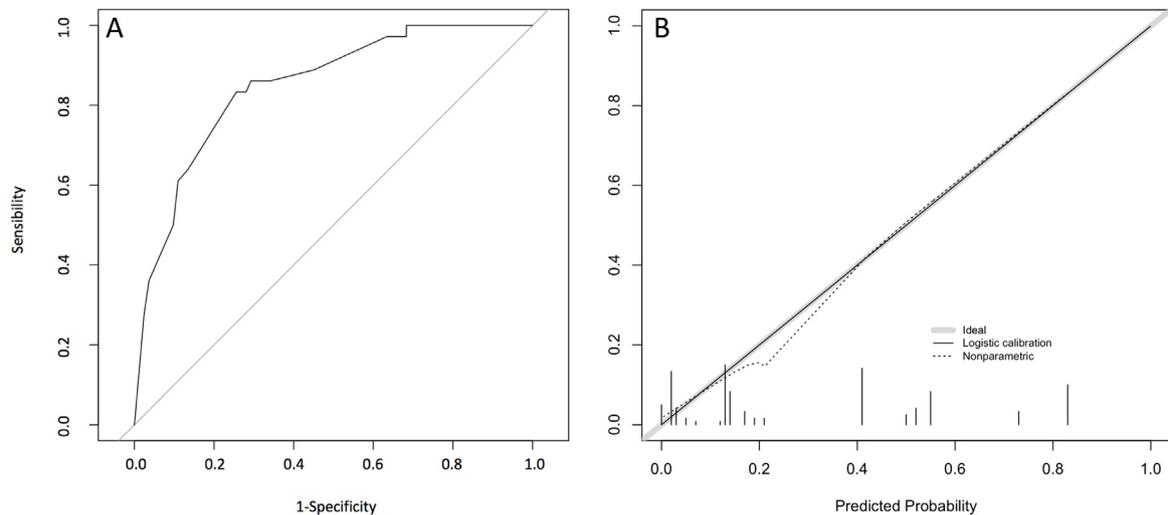
As no randomized controlled trials have been published comparing first-line MAR to first-line surgery in women with DIE-related infertility without bowel involvement, fertility management strategies are mainly based on retrospective studies [17]. However, the LBR and PR for infertile women who conceive spontaneously or following MAR after surgery are heterogeneously reported in literature [17]. In view of these confusing data, the indication of surgery for women with DIE without bowel involvement who are considering MAR remains somewhat blurred [4]. In contrast, for the subset of women for whom spontaneous conception is planned, complete removal of DIE lesions seems to be associated with a significant improvement in fertility outcome. In the present study, we specifically focused on defining predictive factors associated with LBR and PR in the sub-population of

symptomatic infertile women who underwent a first surgical management for DIE without bowel involvement. We report an overall PR and LBR of 30.5% and 39%, respectively which is in discordance with previous literature reports [17]. In their recent literature review, in the specific group of women with DIE without bowel involvement who underwent surgery, Cohen et al [17] reported an overall PR (spontaneous and MAR) of 68.5% (compared to 39.8% in our study) and a spontaneous PR of 50.5% (compared to 66% in our study). These discrepancies should be interpreted with caution for the following reasons: (i) the review was based on heterogeneous studies with few details about the precise extent and location of DIE lesions, and (ii) the studies contained little information concerning the length of postoperative follow-up and the general characteristics of the patients, in particular the etiology of infertility. In the present study, 48% of the 25 patients who underwent MAR became pregnant. This PR is similar to that reported by Mounsambote et al [18] in a study comparing IVF PR in a surgical (40%) and non-surgical (41%) group for infertile patients with DIE without bowel involvement ( $p = 1$ ). Our PR after MAR is also similar to that reported by Capelle et al. [19] evaluating the results of IVF according to the extent of DIE and of lesion removal. However, it is difficult to compare our results with those of Capelle et al. because of the differences in the populations studied: in our series, the endometriotic lesions were always completely removed while some patients in the Capelle et al. study underwent incomplete surgery; in addition, our population only included patients with DIE without bowel involvement which was not the case for the Capelle et al. study.

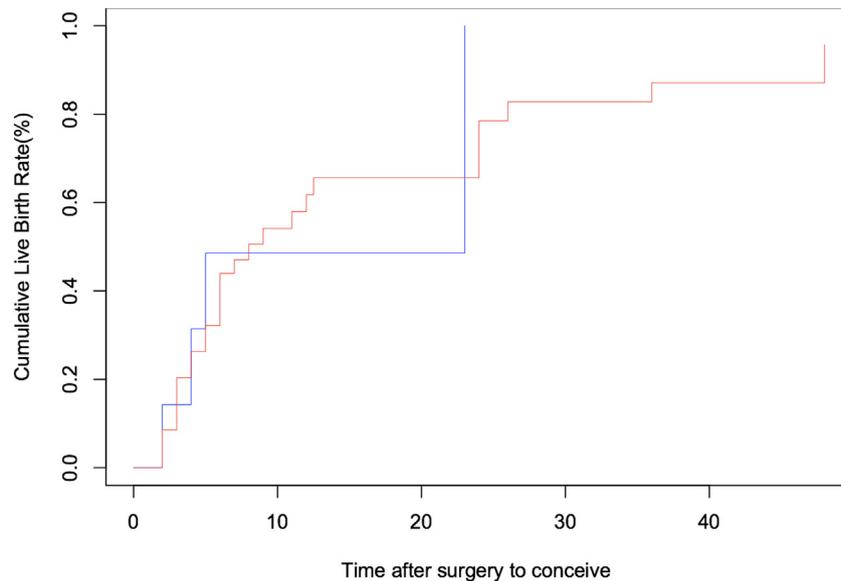
Our clinical end-point, i.e. the likelihood of a live birth, is relevant as it is currently unclear how to best manage infertile women with DIE without bowel infiltration. The nomogram we present here should help physicians identify which women have a good chance of giving birth after spontaneous conception and which women would benefit from MAR. On this topic, the ESHRE guidelines state that the effectiveness of surgical excision of deep nodular lesions before treatment by ART in women with endometriosis-associated infertility is not well established in terms of reproductive outcome [20,21]. The benefit of first-line surgery is only considered in infertile women with AFS/ASRM Stage I/II endometriosis undergoing laparoscopy prior to

**Table 3**  
Multivariate analysis.

Variable	Multivariate analysis OR (95% CI)	P-value
Age (years)		
≤ 30	Reference	
30–35	0.55 (0.05–5.73)	
≥ 35	0.14 (0.04–0.48)	0.0024
BMI (kg/m <sup>2</sup> )		
≥ 25	Reference	
< 25	5.1 (1.05–24.3)	0.029
AMH (ng/ml)		
< 1	Reference	
≥ 1	2.56 (0.21–30.7)	0.44
Enzian score		
Grade 1	Reference	
Grade 2	0.25 (0.07–0.82)	
Grade 3	0.03 (0.007–0.14)	<0.001



**Fig. 2.** A- ROC curve of the model, B- Calibration of the nomogram to predict the LBR in women with DIE without bowel involvement surgery. The discrimination accuracy of the model was 0.84 (95% CI, 0.82–0.86). There was no difference between the predicted probabilities and the observed LBRs ( $P = 0.3829$ ).



**Fig. 3.** Cumulative LBR according to the optimal threshold ( $p < 0.001$ ) for the overall population.

treatment with ART. For these women complete surgical removal of endometriosis to improve the LBR is recommended, although the benefit has not been well established [22]. In 2010, Adamson et al [6] published a prediction model of spontaneous pregnancy after surgery – the Endometriosis Fertility Index (EFI) – including factors such as age, length of infertility, previous pregnancy and surgical factors. The index has been externally validated three times [23–25], and supports the prognostic relevance of laparoscopic surgery in endometriosis-related infertile patients. The main limitation of the EFI score is that it is based on the AFS score and thus only considers superficial endometriosis and not DIE, which is the main clinical challenge. In contrast, our study provides an accurate and evidence-based tool to help physicians determine the likelihood of pregnancy and live birth in women with DIE-related infertility and without bowel involvement. We define according to the threshold good candidate for spontaneous conception a LBR 1.7% vs 50.0% under and above the threshold of 20%.

The current study is the first to establish a correlation between the Enzian score and fertility. The recent consensus published by the World Endometriosis Society [5] on the classification of endometriosis, recommends the use of the rASRM classification and the Enzian score to standardize practice. While no study has been published to date on Enzian and fertility, the authors suggest that the Enzian score has a low predictive ability to detect a woman's response to infertility treatment. However, in the present study, we report that women who conceive after surgery were more likely to have a Grade 3 Enzian score ( $p < 0.0001$ ). This would indicate that surgery should be recommended for women with a low score (Grade 1). In our nomogram, the Enzian score emerges as the most relevant factor influencing the probability of a live birth. Further studies are thus needed to assess the true relevance of the Enzian score as a predictive factor for fertility. In our study, the Enzian score was calculated during surgery but Di Paola et al. [26] have shown that MRI correlates with the Enzian score with an accuracy of 95% in the detection and localization of DIE, thus

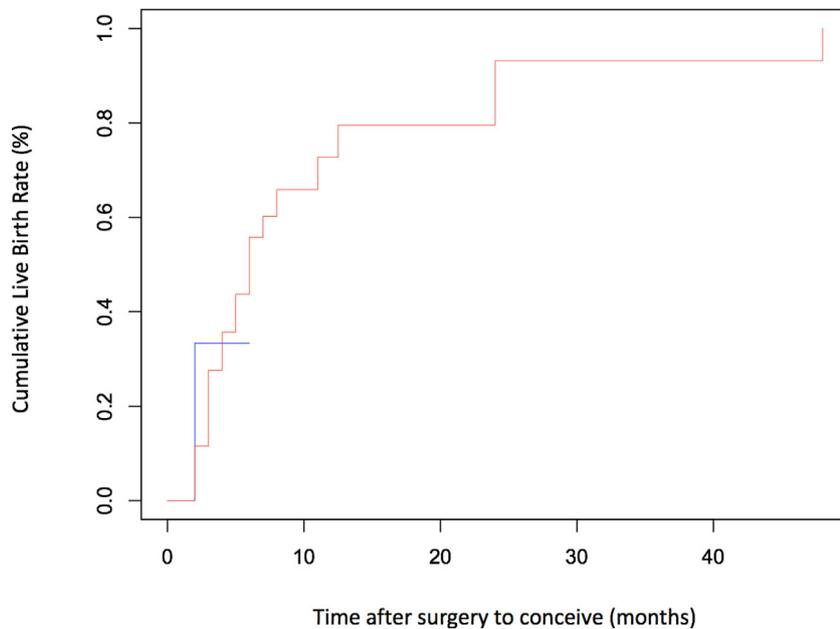


Fig. 4. Cumulative LBR according to the optimal threshold ( $p < 0.001$ ) for women who conceived spontaneously.

minimizing false negative results (4%) in patients with DIE and obtaining a good preoperative staging. Extrapolating these results, we could consider that a pre-operative MRI Enzian score should be calculated for all patients before surgery to evaluate its relevance for women who wish to conceive, using our nomogram. In the future, the use of pre-operative data will become the first step in the surgery decision process. This cannot be done with the rASRM score.

In light of recent advances in fertility preservation techniques (FPT), such as oocytes and ovarian tissue freezing, the options for FPT in patients suffering from endometriosis should be considered. Because of possible loss of ovarian reserve due to surgery and/or presence of endometriomas, personalized counseling should be offered to all patients with endometriosis taking into account age, extent of ovarian involvement, AMH, previous and impending surgeries for endometriosis, along with current success rates and possible risks associated with FPT [27].

The main limitation of our study is its retrospective nature and the long period of data collection. Furthermore, pre-operative assessment of AMH levels, a test which is not reimbursed by the French Health System, was not performed in all patients due to the cost.

This work presents the originality of describing the fertility and the live birth rate after surgery for DIE without bowel involvement with a predictive model. It aims to improve information to the patient, discuss the benefit-risk balance of surgical treatment in case of infertility.

#### Contribution to authorship

Alexandra ARFI (AA): planner, designer, data acquisition, writer, analyser

Sofiane Bendifallah (SB): planner, designer, data acquisition, writer, analyser

Emmanuelle Mathieu d'Argent (EMDA) : analyser

Clothilde Poupon (CP) : data acquisition

Marcos Ballester (MB): analyser, critical discussion

Jonathan Cohen (JC): analyser, critical discussion

Emile Darai (ED): planner, designer, analyser

#### Details of ethics approval

Prospective recording of data was approved by the French authority CCTIRS (Advisory Committee on Information Processing in Healthcare Research) CEROG 2012-GYN-10-03. All the women gave their informed consent.

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