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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

Alexandra ARFI (MD), Sofiane BENDIFALLAH (MD, PhD), Emmanuelle MATHIEU D'ARGENT (MD), Clothilde POUPON (MD), Marcos BALLESTER (MD, PhD), Jonathan COHEN (MD, PhD), Emile DARAI (MD, PhD)

STRUCTURED 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 woman had a LB (30.5%). In multivariate analysis, factors associated with a LB were: age ≤ 30 years ($p = 0.0024$), BMI ≤ 25 kg / m² ($p = 0.029$) 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.

Keywords: Medically assisted reproduction / endometriosis without bowel involvement / nomogram / prediction models / Live birth

1   **_Introduction**

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

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

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

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

16

17

18 **Materials and Methods**

19   We conducted a retrospective analysis of our database using information from
20 women with DIE without bowel involvement who wished to conceive and who underwent
21 surgery from January 2006 to December 2014 at Tenon University Hospital in Paris, France.

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

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

30

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

40

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

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

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

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

68 The categorical and numerical variables were analyzed using the χ^2 test and the
69 Student t test, respectively. Differences were considered significant at a P-value of .05. All
70 analyses were performed using the R package with the Design, Hmisc, Design,
71 Presence/absence ([http:// lib.stat.cmu.edu/R/CRAN](http://lib.stat.cmu.edu/R/CRAN)).

72

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

76

77 **RESULTS**

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

87 ligaments, 36 patients (30.6%) required a cystectomy for endometrioma and 24 patients a
88 colectomy (20.3%).

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

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

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

104

105 A BMI >30 kg/m² ($p=0.017$), and an AMH serum level >2 ng/ml ($p=0.0006$) were
106 predictive factors for obtaining a spontaneous pregnancy compared to a MAR pregnancy
107 (Table 2). PRs at 12 and 24 months were similar in both groups (no statistically significant
108 difference).

109

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 (Figure 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 (Figure 2-A).

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 (Figure 2-B).

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. Figure 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. Figure 4 highlights the cumulative LBR according to the optimal threshold ($p < 0.001$) for women who conceived spontaneously.

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

181 deep nodular lesions before treatment by ART in women with endometriosis-associated
182 infertility is not well established in terms of reproductive outcome (20,21). The benefit of
183 first-line surgery is only considered in infertile women with AFS/ASRM Stage I/II
184 endometriosis undergoing laparoscopy prior to treatment with ART. For these women
185 complete surgical removal of endometriosis to improve the LBR is recommended, although
186 the benefit has not been well established (22). In 2010, Adamson et al (6) published a
187 prediction model of spontaneous pregnancy after surgery – the Endometriosis Fertility Index
188 (EFI) – including factors such as age, length of infertility, previous pregnancy and surgical
189 factors. The index has been externally validated three times (23–25), and supports the
190 prognostic relevance of laparoscopic surgery in endometriosis-related infertile patients. The
191 main limitation of the EFI score is that it is based on the AFS score and thus only considers
192 superficial endometriosis and not DIE, which is the main clinical challenge. In contrast, our
193 study provides an accurate and evidence-based tool to help physicians determine the
194 likelihood of pregnancy and live birth in women with DIE-related infertility and without
195 bowel involvement. We define according to the threshold good candidate for spontaneous
196 conception a LBR 1.7% vs 50.0% under and above the threshold of 20 %.

197   The current study is the first to establish a correlation between the Enzian score and
198 fertility. The recent consensus published by the World Endometriosis Society (5) on the
199 classification of endometriosis, recommends the use of the rASRM classification and the
200 Enzian score to standardize practice. While no study has been published to date on Enzian
201 and fertility, the authors suggest that the Enzian score has a low predictive ability to detect a
202 woman's response to infertility treatment. However, in the present study, we report that
203 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. (31) have shown that MRI correlates with the Enzian score with an accuracy of 95% in the detection and localization of DIE, thus 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 (32).

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
Clotilde 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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LEGENDS FOR FIGURES AND TABLES

Figure 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.

Figure 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 ($P=0.3829$).

Figure 3: Cumulative LBR according to the optimal threshold ($p<0.001$) for the overall population

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

Table 1: Characteristics of the overall population

Table 2: Characteristics of the population according to the type of pregnancy

Table 3 : Multivariate analysis

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^b
Mean age at diagnosis (range):		30.8 (22-42)	28.6 (19-40)	
Age ≤ 30 years:				
- Yes	63 (53.4)	38 (46.3)	25 (69.4)	0.02
- No	55 (46.6)	44 (53.7)	11 (30.6)	
BMI ≥ 25 kg/m²:				
- Yes	19 (16.1)	16 (19.5)	3 (8.3)	0.15
- No	89 (75.4)	60 (73.1)	29 (80.5)	
- NA ^a	10 (8.5)	6 (7.4)	4 (11.1)	
Smoking				
- Yes	32 (27)	19 (23.2)	13 (36.1)	0.09
- No	66 (56)	50 (61)	16 (44.4)	
- NA	20 (17)	13 (15.8)	7 (19.4)	
Infertility prior surgery				
- Yes	66 (56)	47 (57.3)	19 (52.8)	0.65
- No	52 (44)	35 (42.7)	17 (47.2)	
Prior surgery for endometriosis				
- Yes	26 (22)	17 (20.7)	9 (25)	0.61
- No	92 (78)	65 (79.3)	27 (75)	
MRI: adenomyosis				
- Yes	17 (14.4)	10 (12.2)	7 (19.4)	0.25
- No	99 (83.9)	72 (87.8)	27 (75)	
- NA	2 (1.7)	0 (0)	2 (5.6)	
Enzian score				
- Grade 1	46 (39)	21 (25.6)	25 (69.5)	<0.0001
- Grade 2	27 (22.9)	19 (23.2)	8 (22.2)	
- Grade 3	45 (38.1)	42 (51.2)	3 (8.3)	
ASRM score				
- I/II	42 (35.6)	29 (35.4)	13 (36.1)	0.94
- III/IV	76 (64.4)	53 (64.6)	23 (63.9)	0.39
- median	/	37	30	
Surgical route				
- Laparoscopy	118 (100)	82 (100)	36 (100)	1
Surgery resection: torus and/or utero-sacral ligaments				

- Yes	82 (69.5)	60 (73.2)	22 (61.1)	0.19
- No	36 (30.5)	22 (26.8)	14 (38.9)	
Surgery resection: torus and/or utero-sacral ligaments and cystectomy				
- Yes	36 (30.5)	22 (26.8)	14 (38.9)	0.19
- No	82 (69.5)	60 (73.2)	22 (61.1)	

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

^aNA, not available

^bUnivariate 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
Age (year): ≤30 median, range - Yes - No	30 (19-41) 22 (71) 9 (29)	28.5 (22-38) 10 (62,5) 6 (37,5)	0.86 0,55
BMI (kg/m²) >30 median, range - Yes - No - NA	22 (17-29) 0 (0) 27 (87.1) 4 (12.9)	21 (16-30) 3 (18.8) 12 (75) 1 (6.2)	0.44 0.04
Tobacco - Yes - No - NA	8 (25.8) 19 (61.3) 4 (12.9)	6 (37.5) 6 (37.5) 4 (25)	0.28
Prior surgery for endometriosis	7 (22.6)	6 (37.5)	0.28
AMH (ng/ml) median, range - <2 - <1 - NA	3.6 (1-6,1) 1 (3.2) 0 (0) 12	3.1 (0.48-6.7) 6 (37.5) 2 (12.5) 7	0.08 0.0004 0.03
MRI : adenomyosis	5 (16.1)	4 (25)	0.46
rASRM total score: median, range - Stade I, II - Stade III, IV	20 (4-124) 12 (38.7) 19 (61.3)	50 (4-114) 5 (31.2) 11(68.8)	0.52 0.61 0.61
ENZIAN score - Grade 1 - Grade 2 - Grade 3	24 (77.4) 6 (19.4) 1 (3.2)	9 (56.2) 3 (18.8) 4 (25)	0.07

Surgery resection: torus and/or utero-sacral ligaments	22 (71)	8 (50)	0.09
Pregnancy rate at 12 months	24 (77.4)	9 (56.3)	0.18
Pregnancy rate at 24 months	29 (93.5)	12 (75)	0.25

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 ²)		
≥ 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