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Predicting the likelihood of a live birth for women with endometriosis-related infertility.

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Predicting the likelihood of a live birth for women with endometriosis-related infertility:
abstract (350 words)

Objective: Endometriosis affects 10% of women in reproductive age and alters fertility. Its management is still debated notably the timing of surgery and ART in infertility. Several tools have been created to guide the practitioner and the couple yet many limitations persist. The objective is to create a nomogram to predict the likelihood of a live birth after surgery followed by assisted reproductive technology (ART) for patients with endometriosis-related infertility.

Study design: All women in a public university hospital who attempted to conceive by ART after surgery for endometriosis-related infertility from 2004 to 2016 were included. We created a model using multivariable linear regression based on a retrospective database.

Result: Of the 297 women included, 171 (57.6%) obtained a live birth. Age, duration of infertility, number of ICSI-IVF cycles, ovarian reserve and the revised American Fertility Society (rAFS) score were included in the nomogram. The predictive model had an area under the curve (AUC) of 0.77 (95% CI, 0.75–0.79) and was well calibrated. The external validation of the model was achieved with an AUC of 0.71 (95% CI, 0.69–0.73) and calibration was good. The staging accuracy according to AUC criteria for the nomogram compared to the currently used Endometriosis Infertility Index to predict live births were 0.77 (95% CI, 0.75–0.79) and 0.60 (95% CI: 0.57-0.63), respectively.

Conclusion: This simple tool appears to accurately predict the likelihood of a live birth for a patient undergoing ART after surgery for endometriosis-related infertility. It could be used to counsel patients in their choice between spontaneous versus ART conception, or oocyte donation.

Keywords

Endometriosis; Endometriosis Infertility Index; Infertility; Live birth; Nomogram

Introduction

Endometriosis is a chronic gynecologic disorder defined by the ectopic occurrence of endometrium-like tissue which causes local inflammation and is associated with pelvic pain and infertility (1). Although the true prevalence of endometriosis is unknown, it has been estimated at 10% in women of reproductive age (2).

Despite international guidelines, the management of endometriosis-related infertility remains a matter of debate. Two randomized controlled trials (3,4), a subsequent systematic review (5) and other non-randomized studies have suggested that the removal of minimal, mild and deep endometriosis (DE) improves the chances of pregnancy both by spontaneous conception and after Assisted Reproductive Technology (ART) (intra-cytoplasmic sperm injection (ICSI)-in vitro fertilization (IVF)) (6–11)

To date, two tools have been developed to predict fertility outcomes for either spontaneous conception or ART in women with endometriosis-related infertility: the Endometriosis Fertility Index (EFI) and the revised American Society for Reproductive Medicine (rASRM) classification of endometriosis (12). However, the EFI score (i) can only stratify patients rather than provide individual predictions of the likelihood of pregnancy, (ii) does not distinguish between pregnancy and the more relevant outcome of a live birth, (iii) it is not specifically designed to take into account minimal, mild or DE cases, where the greatest controversy exists and, (iv) finally, its accuracy has never been compared with a predictive tool such as a nomogram for women referred for ART (ICSI-IVF) after the surgery. As regards the rASRM classification, its use alone to predict pregnancy has not been proved (13).

Predicting the specific likelihood of a live birth after ART following surgery could be useful to help the practitioner decide on the optimal postoperative management of endometriosis-related infertility. Therefore, the aim of the present study was to develop a nomogram to predict the likelihood of a live birth after surgery followed by ART (ICSI-IVF)

for women with endometriosis-related infertility.

Materiel and method

Training cohort

The data of all patients with endometriosis-related infertility were extracted from a prospectively maintained database in a tertiary care center: Jean Verdier University Hospital (France) from 2004 to 2016. We included patients who had undergone primary surgical management of endometriosis followed by ART.

Data regarding history of infertility, previous symptoms and surgery, the extent of endometriosis, postoperative management of infertility and fertility outcomes (pregnancy rate (PR), live-birth rate (LBR)) were collected. Informed consent was obtained from each patient before beginning the surgery. The Ethics Committee of Jean Verdier University Hospital approved the study protocol (JVR93140-09- 2012).

Patients presenting a spontaneous pregnancy after surgery or DE with bowel involvement were excluded.

Surgical management

All laparoscopies were performed by two experienced surgeons (C.P or J.B.) with the intention to remove all endometriotic lesions. Indications for laparoscopy were pelvic pain, abnormal hysterosalpingogram or unexplained infertility. Surgery was never performed for the sole purpose of staging. Complete pelvic adhesiolysis was performed. Superficial peritoneal endometriotic lesions were treated by ablation (electrocoagulation, plasma ablation or excision). Endometriomas were treated either by plasma ablation (<3 cm or pre-operative diminished ovarian reserve) or by cystectomy or plasma ablation (>3 cm and normal ovarian reserve). Cycle length, antral follicle count (AFC) and serum anti-Mullerian hormone (AMH) were assessed to evaluate ovarian function as well as ultrasonography on Day 12 to determine folliculogenesis and ovulation. The revised American Fertility Society (rAFS) score, rASRM

staging and the EFI score were collected after surgery. Patients were considered to have a poor ovarian reserve when the AFC was < 8 , the follicle stimulating hormone (FSH) $> 14\text{mIU/l}$, the AMH $< 1\text{ng/ml}$, and in the case of a short follicular phase or no response to stimulation.

ART procedures

Women were monitored and managed according to the hospital's clinical protocols. Various controlled ovarian stimulation (COS) protocols were used, with 150–450 IU/day of recombinant FSH or human menopausal gonadotropin in a gonadotropin-releasing hormone antagonist protocol, a long agonist protocol, or a short agonist protocol. The protocols were determined according to each patient's characteristics (age, body mass index (BMI), AFC and AMH). Transvaginal oocyte retrieval was scheduled 35–36 h after hCG injection. ART was performed per standard operating procedure of the hospital. Fertilization was assessed by the appearance of two pronuclei. Cleavage stage embryos were graded as per the Istanbul consensus. Fresh embryo transfer (ET) was performed 2–3 or 5 days later. Embryos were vitrified or slow frozen on day 2, 3 or 5. Only top quality embryos were frozen. The luteal phase was supported by vaginal administration of micronized progesterone (400 mg/d) started on the day of ovarian puncture.

Outcomes

The primary endpoint was the LBR. The PR was also assessed. A pregnancy was defined by a b-hCG level $> 25\text{ UI/L}$. A live birth was defined as a live delivery > 25 weeks of gestation.

Statistical analysis

Development of the model:

We developed a nomogram to predict patient-specific likelihoods of LBR in women with endometriosis-related infertility who underwent surgery followed by ART. Backward variable selection was performed to determine independent predictors. Multivariate analysis was performed using the logistic regression model and including the variables that were significant at univariate analysis. A P-value of 0.05 was considered significant.

Values for each of the model covariates were mapped to points on a scale ranging from 0 to 100. The total points obtained for each model corresponded to the probability of an LBR. The predictive accuracy of the model was assessed by its discrimination and calibration (14).

Validation of the model:

An external and internal validation (with 200 bootstrap resamples to obtain relatively unbiased estimates) was performed. 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 area under the curve (AUC). Calibration was assessed using plots that overlap the prediction model. A student-t test and chi 2 test were used to compare the continuous and categorical values, respectively. A P-value of 0.05 was considered significant. The Kaplan–Meier method was used to estimate the odds ratios (ORs).

For external validation, the model was applied to data from a sample of 106 patients (validation set). Data of all patients with endometriosis-associated infertility undergoing ART after surgery between 2010 and 2016 were abstracted from three institutions in France with maintained endometriosis databases (Tours, Rouen and Rennes hospital). Patients were included if they had available data for the components of the model and respected the inclusion criteria of the study.

The accuracy of the EFI and the present nomogram were evaluated with respect to

discrimination.

All statistical analyses were carried out using an Excel database and Rstudio version 1.1.447.

Results

Characteristics of the population

Data of 609 women were extracted from the database for the study period. Of these, 297 underwent ART after surgery for endometriosis-related infertility (Figure 1). The median age of the included patients was 32 years (range 22-41) and the mean BMI was 23.88 kg/m². The average duration of preoperative infertility was 40 months (range 8–192 months).

Epidemiological, clinical, biological characteristics and therapeutic strategies of the training and validation cohorts are summarized in Table 1.

Outcomes

The median time to conception was 20 months (mean 15.9, range 4-41 months). The total number of ICSI-IVF cycles was 867 (median number per patient was two, range: 1-14). The PR and LBR were 73.4% (218/297) and 57.6% (171/297), respectively. The overall cumulative LBR was 26% after one ICSI-IVF cycle, 38% after two cycles and 49% after three cycles.

According to the EFI score, at 36 months 5.1% of patients had a predicted PR after ART of 10% (15/297 had a score between 0-3), 6.7% a predicted rate of 25% (20/297 with a score of 4), 6.4% a predicted rate of 40% (19/297 with a score of 5), 19.5% a predicted rate of 53% (58/297 with a score of 6), 43.8% a predicted rate of 65% (130/297 with a score between 7-8), and 18.5% a predicted rate of 75% (55/297 with a score between 9-10).

Likelihood of a live birth

Table 2 summarizes univariate and multivariate analysis. After multivariate analysis, ovarian reserve and number of ICSI-IVF cycles were significantly related with the likelihood of a live birth. Age, duration of infertility, and rAFS scores were not statistically significantly

related with the LBR but were included in the predictive model due to their clinical relevance. The nomogram derived from this multivariate logistic regression model is presented Figure 2.

Validation of the model

Discrimination: The predictive model had an AUC of 0.77 (95% CI, 0.75–0.79) before the 200 repetitions of bootstrap sample corrections and 0.74 (95% CI, 0.72-0.76) afterwards (Figure 3).

Calibration: No significant difference was noted between the predicted probability obtained from the bootstrap correction and the actual probabilities of a live birth ($P=1$) (Figure 3). The average and maximal differences in predicted and calibrated probabilities were 0.027% and 0.089%, respectively.

After external validation the AUC was 0.71 (95% CI, 0.69–0.73). The calibration plot is summarized in Figure 4.

Comparison accuracy

The staging accuracy according to AUC criteria for the present nomogram and EFI classifications for live birth prediction after ART were 0.77 (95% CI, 0.75–0.79) and 0.60 (95% CI: 0.57-0.63), respectively.

Comments

To the best of our knowledge, the nomogram we present here is the first to predict the likelihood of a live birth after surgery for endometriosis followed by ART (ICSI-IVF) for women with endometriosis-related infertility. Its value lies in the combination of readily available clinical, biological and surgical characteristics, namely: age at diagnosis, duration of infertility, ovarian reserve, number of ICSI-IVF cycles and the rAFS score. In addition, AUC assessment suggests that the model is more accurate than the EFI score for predicting the LBR. Another advantage of the nomogram lies in its dynamic nature: the model takes into account the number of ICSI-IVF cycles which influences the LBR and therefore reflects changes in the probability of a live birth during a patient's ART course. We hypothesize that the nomogram can be used in routine practice to facilitate patient counseling, especially for women with poor prognosis who need to make a swift, informed decision about their fertility strategy and consider oocyte donation.

Over the last decade, ART has become the most suitable approach for women with endometriosis-related infertility. Surgery and ART are not mutually exclusive and a significant proportion of women with endometriosis-related infertility thus choose to undergo surgery not to improve their chances of pregnancy but to improve their quality of life (15). For these women, the real question is not whether surgery is superior to ART in first line, but rather what their real chances of giving birth are. After surgery followed by ART, we observed that 73.4% (218/297) and 57.6% (171/297) of women had a pregnancy and live birth, respectively. These results are in accordance with previous studies (16) and the review by Cohen et al. suggests an overall postoperative PR of 68.3% in women with endometriosis-related infertility without bowel involvement (17). Hence, we hypothesize that, similarly to the EFI score used to define the spontaneous PR after surgery, our results are of interest for

infertile women who undergo ART after surgery to adopt a personalized ART strategy and obtain information concerning their specific fertility outcome. Both the internal and external validations of the tool are statistically robust.

Several unresolved issues remain when managing women with endometriosis-related infertility with: (i) low ovarian reserve, and/or (ii) absence of ovarian response to hyperstimulation, and/or (iii) repeated failures of ART. A major topic of controversy is when to introduce oocyte donation which is often the last opportunity to conceive. Although published data on the subject are sparse, it has been reported that PRs are similar for women with endometriosis as for women with other indications, if endometrial preparation is appropriate(18). Hence, we hypothesize that the added value of the present tool could be to identify women with a poor probability of a live birth for whom oocyte donation would appear to be the most suitable option. The present nomogram could thus be used to inform couples early on about this option which is especially important in view of the long waiting times related to the shortage of donors in France.

Several prognostic factors have been reported for endometriosis-related infertility. Patient age is frequently involved in assessing the probability of a live birth or pregnancy (19). Our results suggest its interest only in univariate analysis. We nevertheless opted to use “age” as a predictor due to its clinical relevance. In addition, we chose to include “low ovarian reserve” in the model (i.e., low AMH levels(20), and/or elevated FSH (21) and/or low AFC(22)) as this was demonstrated to be a strong factor related to fertility outcomes after ART by the European Society for Human Reproduction and Embryology (ESHRE) (23). As previously published, the number of ICSI-IVF cycles increases the PR and LBR in infertile women(24), especially for women with endometriosis-related infertility(25). Although the rAFS score was not statistically significant, we also included it in our model due to its clinical interest. The rAFS score has long been a reference to classify the severity of endometriosis-

related infertility and to guide treatment (26,27). Its role in predicting PR is not so clear due to its low correlation with the likelihood of pregnancy (28). However, we chose to include this score to optimize the external validity with a criterion used worldwide. Finally, the recent consensus published by the World Endometriosis Society (29) on the classification of endometriosis, recommended the use of the rASRM classification and the Enzian score to standardize practice.

The main limitation of our study is its retrospective nature and the long period of data collection. Furthermore, preoperative assessment of AMH levels, a test that is not reimbursed by the French Health System, was not performed in all patients due to the cost. In addition, the unit's protocols evolved throughout the long study period, particularly for ART management approaches. A third limitation is related to potential selection bias due to the center: the Gynecologic and Obstetrics Department of the Jean Verdier Hospital is an expert center for endometriosis. We therefore see women with more severe forms of endometriosis, often with a surgical history, and subsequently with a poorer fertility prognosis than other centers. All surgeries were performed by two surgeons, which can limit the generalizability of this study. However, the patients from the validation set were extracted from three centers with different surgeons with a strong external validation. We chose to exclude patients with endometriosis and bowel involvement to reduce the bias induced by the negative impact of digestive involvement in endometriosis-related infertility and the likelihood of a pregnancy (6,25). We decided to exclude these patients in the interest of forming a homogeneous group. Moreover, to our surprise, type of endometriotic surgery (endometrioma, deep or superficial endometriosis) was not associated with LBR.

Conclusion

Our analysis suggests that the nomogram we present here can predict an individual probability of a live birth after ART in women with endometriosis-related infertility. This score, which is simple and clinically pertinent, could help patients make an informed decision in their infertility course.

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Figure legends

Figure 1: Flow chart of training cohort

Figure 2: Nomogram predicting the likelihood of live birth in patients with endometriosis-related infertility without bowel involvement undergoing first line ART after surgery.

The probability of a live birth is calculated by drawing a line to the corresponding point on the axis for each of the following variables: age, duration of infertility, ovarian reserve, ICSI/IVF cycles and AFSR score. The points accumulated by the covariates are summed up and correspond to the “total points”. 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 3: Discrimination and validation of the model predicting the likelihood of a live birth in patients with endometriosis-related infertility without bowel involvement undergoing first line ART after surgery

- A. ROC curve of the model. The predictive model had an AUC of 0.77 (95% CI, 0.75–0.79).
- B. Calibration of the model. The horizontal axis represents the predicted probability of a live birth and the vertical axis represents the actual probability of live birth. Perfect prediction would correspond to the 45-degree broken line. The dotted and solid lines indicate the observed (apparent) nomogram performance before and after bootstrapping.

Figure 4: External validation of the nomogram using the validation cohort.

- A. ROC curve of the validation cohort. The AUC was of 0.71 (95% CI, 0.69–0.73).
- B. Calibration of the validation cohort

Figure 1: Flow chart of training cohort

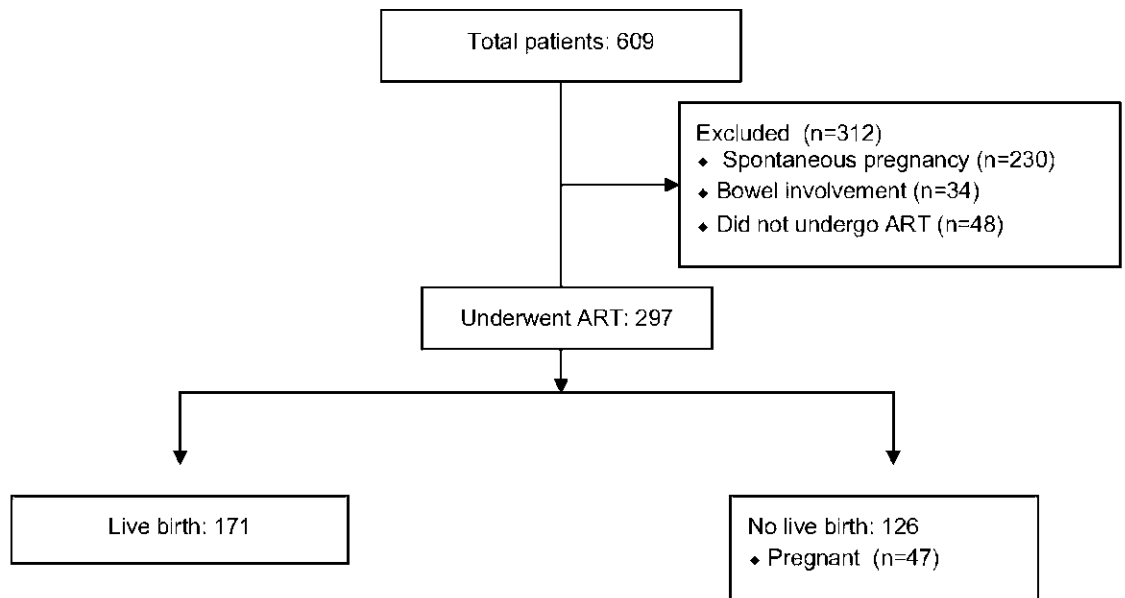
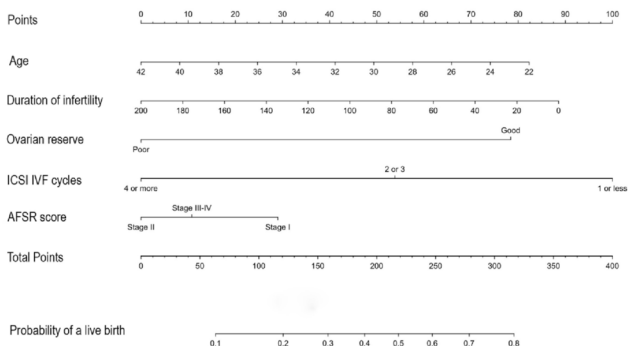


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Abbreviations: rAFS= revised American Fertility Society, IVF= In Vitro Fertilization, ICSI= Intracytoplasmic Sperm Injection

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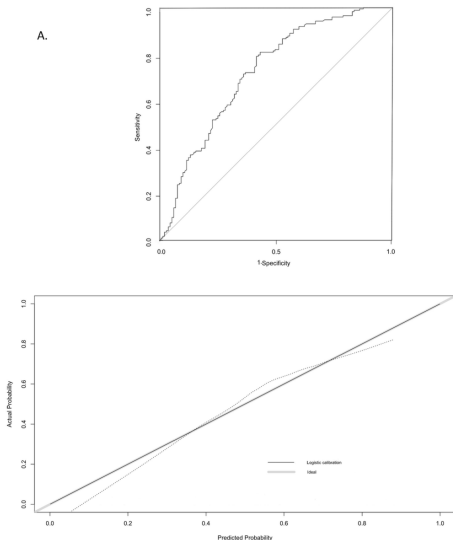
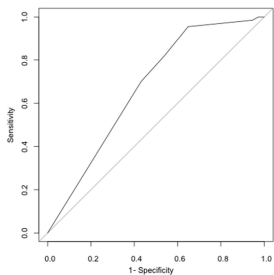


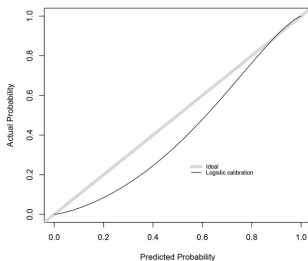
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B. Calibration of the validation cohort



A.



B.

Table I. Patient characteristics in the training cohort (N=297) and validation cohort (N=106)

Characteristics		Training cohort N=297 (%)	Validation cohort N=106 (%)	P-value
Live birth		171 (57.6)	63 (59.4)	0,96
Pregnancy rate		218 (73.4)	68 (64.2)	0.11
Age (years old)	Mean +/- SD	32.23 +/- 4.4	30.3 +/- 4.6	<0.001
	Median	32	31	
	< 35	214 (72)	94 (88.7)	0.003
	36-39	64 (21. 6)	9 (8.5)	
	> 40	19 (6.4)	3 (2.8)	
BMI (Kg/m ²)	Mean +/-SD	23.88+/- 4.12	24 +/- 4.6	0.96
Infertility length (months)	Mean	40.17 +/-24.6	42.6 +/- 31.3	0.47
	Median	36	32	
	<3 years	123 (41.4)	57 (53.8)	0.072
	≥ 3 years	172 (57.9)	49 (46.2)	
	NA	2 (0.7)	0	
rAFS score	Stage 1	126 (42.4)	24 (22.6)	<0.001
	Stage 2	66 (22.2)	11 (10,4)	
	Stage 3 or 4	105 (35.4)	71 (67)	
ICSI IVF cycles	1	103 (34.7)	65 (61.3)	<0.001
	2-3	93 (31.3)	36 (34)	
	4 or more	101 (34)	5 (4.7)	
	Mean	2.9 +/- 2	1,5 +/- 0.8	
	Median	2	1	
Ovarian reserve	Good	240 (80.9)	83 (78.3)	0.68
	Poor	57 (19.1)	23 (21.7)	
Prior pregnancy	Yes	77 (25.9)	30 (28.3)	0.73
	No	220 (74.1)	76 (71.7)	
AFC	Mean	15.62 +/- 7.8	12.5 +/- 6.5	<0.001
	Median	14	12	
Abnormal hysteroGRAPHY		135 (45.5)	13 (12.3) NA = 17	<0.001
Uterosacral endometriosis		133 (44.8)	60 (56.6) NA = 25	<0.001
Endometriomas		51 (17.1)	51 (48.1) NA = 8	<0.001

