

Nomogram to predict pregnancy rate after ICSI–IVF cycle in patients with endometriosis

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BACKGROUND: Although several scoring systems have been published to evaluate the pregnancy rate after ICSI–IVF in infertile patients, none of them are applicable for patients with deep infiltrating endometriosis (DIE) nor can they evaluate the chances of pregnancy for individual patients. The aim of this study was to develop a nomogram based on an association of patients' characteristics to predict the clinical pregnancy rate in patients with endometriosis.

METHODS: This prospective longitudinal study was conducted from January 2007 to June 2010. The nomogram was built from a training cohort of 94 consecutive patients (141 ICSI–IVF cycles) and tested on an independent validation cohort of 48 patients (83 ICSI–IVF cycles). DIE was confirmed in all participants.

RESULTS: The pregnancy rate (per patient) in women with and without DIE was 58 and 83%, respectively ($P = 0.03$). Increased patient age ($P = 0.04$), serum anti-Müllerian hormone (AMH) level ≤ 1 ng/ml ($P = 0.03$) and increased number of ICSI–IVF cycles ($P = 0.03$) were associated with a decreased clinical pregnancy rate. The presence of DIE was the strongest determinant factor of the clinical pregnancy rate in our model [odds ratio = 0.26, 95% confidence interval (CI): 0.07–0.9 ($P = 0.006$)], which also included patient age, serum AMH level and number of attempts at ICSI–IVF. The nomogram showed an area under the curve (AUC) of 0.76 for the training cohort (95% CI: 0.7–0.8) and was well calibrated. The AUC for the validation cohort was 0.68 (95% CI: 0.6–0.75) and calibration was good.

CONCLUSIONS: Our nomogram provides realistic and precise information about ICSI–IVF success and can be used to guide couples and practitioners.

Key words: IVF / endometriosis / nomogram / prediction models / pregnancy

Introduction

Endometriosis is characterized by the presence of endometrial glands and stroma outside the uterus. It affects ~7% of the general female population—up to 48% in infertile women (ASRM 2004; Nezhat et al., 2008)—and represents a real clinical issue causing pain (Koninckx et al., 1991; Fauconnier et al., 2002) and infertility (Pouly et al., 1996; Fauconnier et al., 2002).

The options for a patient with endometriosis-associated infertility to achieve pregnancy depend on the patient's age, her ovarian reserve and the location of endometriosis. Two randomized studies and a meta-analysis have demonstrated the positive impact on spontaneous fertility of removing endometriotic lesions in patients with Stage I–II

endometriosis as defined by the American Society of Reproductive Medicine (ASRM) (Adamson and Pasta, 1994; Marcoux et al., 1997; Beretta et al., 1998). Moreover, a meta-analysis including patients with ASRM Stage III–IV endometriosis also proved the efficacy of surgery on the pregnancy rate (Adamson and Pasta, 1994). However, this analysis did not take into account deep infiltrating endometriosis (DIE) and debate persists as to whether surgical removal of DIE is effective in improving pregnancy rates. One randomized study suggested no benefit on the pregnancy rate of removal of DIE compared with expectant management (Vercellini et al., 2006). In contrast, several retrospective studies have shown that prior surgery improved both spontaneous and post-ICSI–IVF pregnancy rates, suggesting that surgery should be considered before assisted reproduction therapy

(ART) (Donnez et al., 2002; Suginami et al., 2002; Stepniwska et al., 2009; Barri et al., 2010). Although several scoring systems have been published to evaluate the pregnancy rate after ICSI–IVF in infertile patients, none of them are applicable for patients with DIE and cannot evaluate the chances of pregnancy for individual patients.

The aim of this study was therefore to develop a nomogram to predict the clinical pregnancy rate per patient in patients with and without DIE based on criteria before ICSI–IVF procedure.

Materials and Methods

Patients

From January 2007 to June 2010, 142 women who had undergone ICSI–IVF treatment at Tenon Hospital, Paris, France, were prospectively identified. All of them had been infertile for at least 1 year. Investigation of fertility included a hysterosalpingography, cycle Day 3 serum level measurements of estradiol (E_2), FSH, inhibin B, anti-Müllerian hormone (AMH), transvaginal sonography and semen analysis for the partner. Presence of endometriosis was based on physical examination, transvaginal sonography and magnetic resonance imaging using previously published imaging criteria (Bazot et al., 2004, 2009). All the patients gave informed consent to participate in the study. The protocol was approved by the Ethics Committee of the Collège National des Gynécologues et Obstétriciens Français (CNGOF).

Procedure

Patients were stimulated using a long GnRH agonist protocol for the first cycle. Short agonist or antagonist protocols were chosen for additional cycles in poor responders. Ovarian stimulation was begun once pituitary desensitization (E_2 level <50 pg/ml) had been achieved with doses of recombinant FSH ranging between 75 and 450 IU/day depending on BMI, patient age, size and number of follicles, and E_2 levels. Transvaginal oocyte retrieval was scheduled 35–36 h after hCG injection and embryo transfers performed 2–3 days later. On Day 2, individually cultured embryos were evaluated on the basis of the number of blastomeres, blastomere size, fragmentation rate and presence of multinucleated blastomeres (Scott et al., 2000). Embryos with four regular blastomeres and $<20\%$ fragmentation were defined as top quality embryos. The luteal phase was supported by vaginal administration of micronized progesterone (400 mg/day) from the day of ovarian puncture to the day of the pregnancy test. Pregnancies were diagnosed by an increasing concentration of serum β -hCG, which was tested 14 days after embryo transfer. Clinical pregnancies were confirmed by the presence of a gestational sac on vaginal ultrasound examination during the fifth week.

Statistics

Development of the model

The end-point of the study was the clinical pregnancy rate after an ICSI–IVF cycle. Multivariable logistic regression (MLR) analysis was used to test the association between the clinical pregnancy rate and patients' characteristics.

MLR was used to construct the nomogram. Backward variable selection was performed to determine independent covariates. Variables entered into the model were: patient age, patient BMI, type of fertilization (ICSI or IVF), the total antral follicle count, the presence of endometrioma, the presence of DIE, the number of ICSI–IVF cycles and serum AMH levels (≤ 1 , >1 ng/ml). Variables were eliminated from the model if their removal actually improved the overall quality of the model (as measured by the Akaike information criterion). The P -values in the

multivariable analysis were based on Wald tests. A P -value of <0.05 was considered significant.

Evaluation of the model

The performance of the model was quantified with respect to discrimination and calibration (Cox, 1958; Swets, 1988; Coutant et al., 2009).

Discrimination (i.e. whether the relative ranking of individual predictions is in the correct order) was quantified with the area under the receiver operating characteristic (ROC) curve (Hanley and McNeil, 1982). The area under the curve (AUC) is a summary measure of the ROC that reflects the ability of a test to discriminate the outcomes across all possible levels of positivity. A 95% confidence interval (95% CI) was calculated for the AUC. AUC ranges from 0 to 1 and a model is considered to have a poor, fair or good performance if the AUC lies between 0.5 and 0.6, 0.6 and 0.7 or superior to 0.8, respectively (Swets, 1988).

Calibration (i.e. agreement between observed outcome frequencies and predicted probabilities) was studied from graphical representations of the relationship between the observed outcome frequencies and the predicted probabilities (calibration curves). Calibration curves were constructed by plotting several quantiles of the empirical distribution of the predictive probability (i.e. predicted probabilities) and the frequencies observed in each quantile. A perfectly accurate prediction model would result in a plot where the observed and predicted probabilities fall along the diagonal. Indeed, a calibration curve can be approximated by a regression line with intercept α and slope β . These parameters can be estimated in a logistic regression model with the event as the outcome and the linear predictor as the only covariate. Well-calibrated models have $\alpha = 0$ and $\beta = 1$. Therefore, a sensible measure of calibration is a likelihood ratio statistic testing the null hypothesis that $\alpha = 0$ and $\beta = 1$. The statistic has a χ^2 distribution with two degrees of freedom [unreliability (U) statistic] (Cox, 1958). Individual predictions were calculated from the nomogram. We also evaluated average [E average (E_{aver})] and maximal errors [E maximal (E_{max})] between predictions and observations obtained from the calibration curve (Coutant et al., 2009).

All analyses were performed using the R package with the Design, Hmisc, Rpart and Verification libraries (<http://lib.stat.cmu.edu/R/CRAN/>).

Results

The model was built from a training cohort of 94 consecutive ICSI–IVF patients from January 2007 to February 2009. It was tested on an independent validation cohort of 48 consecutive patients from July 2009 to June 2010.

Patients' and cycle characteristics in the training and validation cohorts are summarized in Tables I and II. The total number of cycles in the training and the validation cohorts was 141 and 83, respectively. There was no difference in the patients' characteristics between the two cohorts except for duration of prior infertility, which was longer in the training cohort ($P = 0.003$). No difference was observed in cycle characteristics between the two groups.

Sixty patients (63.8%) became pregnant in the training cohort (Table II). Among the 34 patients who did not become pregnant, the number of patients who dropped out after the first, second, third and fourth cycle was 18, 9, 4 and 3, respectively. At univariable analysis, duration of prior infertility, BMI, type of infertility (primary versus secondary), prior surgery for endometriosis, type of ART procedure (ICSI versus IVF), associated male infertility and presence of ovarian endometrioma were not associated with the clinical pregnancy rate. The pregnancy rate in patients with and without DIE

Table I Patients characteristics in the training and the validation cohorts.

	Training cohort, N = 94	Validation cohort, N = 48	P-value
Number of cycles	141	83	
Number of cycles per patient-median (range)	1 (1–4)	1 (1–4)	0.2
Age(years)-median (range)	33 (22–42)	33 (26–41)	0.5
BMI (kg/m ²)	21.6 (17.2–36.7)	22.5 (17.6–35.4)	0.7
Patients smoking, n (%)	14 (14.9%)	11 (22.9%)	0.3
Duration (years) of infertility-median (range)	4 (1–11)	3 (1–8)	0.003
Primary infertility, n (%)	76 (80.8%)	36 (75%)	0.5
Associated endometrioma, n (%)	68 (72.3%)	36 (75%)	0.9
Associated DIE, n (%)	62 (66%)	36 (75%)	0.4
Male factor, n (%)	36 (38.3%)	21 (43.8%)	0.6
Prior surgery for endometriosis, n (%)	59 (62.8%)	33 (68.7%)	0.6
Serum AMH level (ng/ml)-median (range)	2.4 (0.4–12.4)	2.9 (0.2–12.1)	0.6

DIE, deep infiltrating endometriosis; AMH, anti-Mullerian hormone.

Table II Cycle characteristics in the training and the validation cohorts.

	Training cohort, N = 94	Validation cohort, N = 48	P-value
COH protocols, n (%)			
Long agonist	67 (71%)	36 (75%)	0.7
Antagonist	9 (10%)	3 (6%)	
Short agonist	18 (19%)	8 (17%)	
Number of ICSI (%)	31 (33%)	19 (39.6%)	0.5
Oocytes retrieved	8 (2–26)	9 (1–22)	0.6
Fresh embryos-median	5 (1–25)	5 (0–15)	0.3
Top Day 2 embryos	1 (0–8)	1 (0–5)	0.5
Day 2 fresh embryos transferred	2 (0–2)	2 (0–3)	0.5
Top Day 2 fresh embryos transferred	1 (0–2)	1 (0–2)	0.9
Day 2 frozen embryos transferred	0 (0–10)	0 (0–6)	0.5
Clinical pregnancy rate per patient	60 (63.8%)	26 (54.2%)	0.35

COH, controlled ovarian hyperstimulation.

was 58 and 83%, respectively ($P = 0.03$). Increased patient age ($P = 0.04$), AMH serum level ≤ 1 ng/ml ($P = 0.03$) and increased number of ICSI–IVF cycles ($P = 0.03$) were associated with a decreased clinical pregnancy rate.

After MLR analysis, the presence of DIE [odds ratio = 0.26, 95% CI: 0.07–0.9 ($P = 0.006$)] was independently associated with the clinical pregnancy rate. Patient age, AMH serum level > 1 ng/ml and number of ICSI–IVF cycles were included in the model as their inclusion improved the overall quality of the model (as measured by the Akaike information criterion).

The equation describing the probability of clinical pregnancy was: $P = 1 / (1 + \exp(-X))$ where $X = 4.89939 - 0.09937 \times V1 - 1.33906 \times V2 + 1.05553 \times V3 - 0.57434 \times V4$, where V1 was the patient's age, V2 the presence of DIE, V3 AMH serum level (0 if ≤ 1 ng/ml and 1 if > 1 ng/ml) and V4 the number of ICSI–IVF cycles. The nomogram derived from this equation is reported in Fig. 1.

The model showed an AUC of 0.76 (95% CI: 0.7–0.8) in the training cohort (Fig. 2), which denotes a good performance. Calibration was good with no significant maximal and average differences (5.5×10^{-9} and $4.4 \times 10^{-2}\%$, respectively) between the predicted probabilities and the observed frequencies.

The AUC of the ROC curve in the validation set was 0.68 (95% CI: 0.6–0.75) indicating a fair performance (Fig. 2). The calibration was acceptable with maximal and average errors of 1.1×10^{-16} and $4.6 \times 10^{-2}\%$, respectively (Fig. 2).

Performance of the model as well as its clinical utility was assessed by the sensitivity, specificity, negative predictive values (NPVs) and positive predictive values (PPVs), and the accuracy (i.e. proportion of true positives and true negatives). In the training set, the threshold which maximizes both the sensitivity and the specificity (i.e. maximizing the number of correctly classified individuals) was 72%. In the validation set, at this threshold of 72%, the sensitivity, specificity, PPV and NPV were 66.7% (95% CI: 42.2–74.6%), 95.7% (95% CI:

82.9–99.8%), 88.9% (95% CI: 56.3–99.4%) and 84.6% (95% CI: 73.3–88.3%), respectively, with a false positive rate of 2.9%, suggesting its clinical relevance.

Discussion

Our analysis of 142 infertile patients with endometriosis resulted in an original model to predict individual clinical pregnancy rates based on

clinically significant data. The nomogram was developed in a training cohort including 94 patients (141 cycles) and tested on an internal independent validation cohort including 48 patients (83 cycles). Performance was evaluated using both calibration and discrimination, and our nomogram outperforms most of the published models (Coutant et al., 2009; Leushuis et al., 2009). The most interesting property of this model is its high PPV, which conveys a good degree of confidence in predicting clinical pregnancy. The resulting nomogram is a user-friendly graphical representation of the model (Fig. 1).

The covariates of our model, including patient age, serum AMH level, presence of DIE and number of ICSI–IVF cycles, are clinically significant and concordant with the published data. Patient age has been reported to be an important prognostic factor in reproductive medicine (Menezo, 2006; Adamson and Pasta, 2010; de Ziegler et al., 2010). Using a cumulative live birth rate per ovarian stimulation cycle to measure the success of IVF, Garrido et al. (2011) demonstrated that women’s age was a negative factor from 35 to 37 years, with a marked decrease in live birth rates beyond age 40 years. Barri et al. (2010) demonstrated that, depending on the age of the patients, the best option for infertile patients with endometriosis was the combination of surgery and IVF. Indeed, for patients aged <35 years, surgery and IVF offered a pregnancy rate of 34.3% compared with only 25.9% in older women. Serum AMH level has also been reported to be a key determinant of pregnancy outcomes. Shebl et al. (2009) found that the mean serum AMH level in women with mild endometriosis (ASRM I–II) was almost equal to that of healthy women while a decrease was observed for patients with

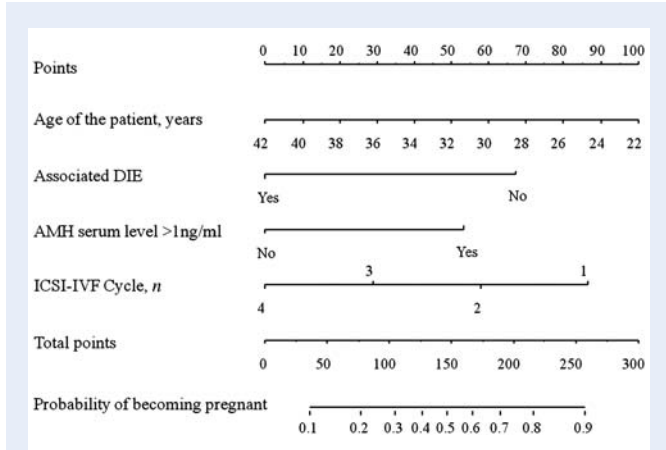


Figure 1 Nomogram to predict clinical pregnancy after an ICSI–IVF cycle; DIE, deep infiltrating endometriosis; AMH: anti-Mullerian hormone.

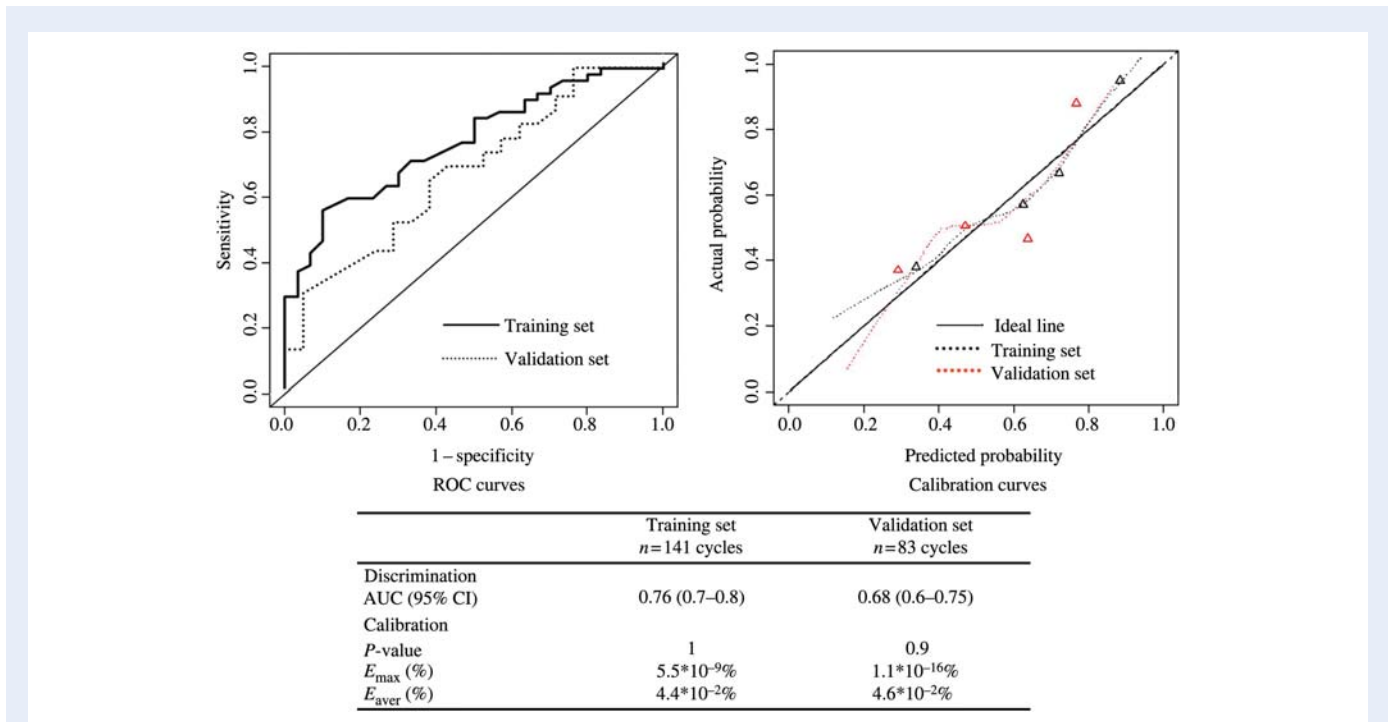


Figure 2 Discrimination and calibration of a model to predict clinical pregnancy in patients with infertility-associated endometriosis. ROC curve of a model to predict clinical pregnancy in patients with infertility-associated endometriosis and calibration curve showing the association between the probability of clinical pregnancy as predicted by the model and the observed clinical pregnancy rate in the training and the validation sets; AUC, area under the ROC curve; CI, confidence interval; E, difference in predicted probability and observed frequencies; E_{max} , maximal error; E_{aver} , average error.

severe endometriosis (ASRM III–IV) although the authors did not take into account the presence of DIE. Buyuk *et al.* (2011) reported that patients with elevated serum AMH levels (≥ 0.6 ng/ml) had twice the number of oocytes retrieved, a greater number of Day 3 embryos and a higher clinical pregnancy rate compared with patients with AMH serum levels below this value. The presence of DIE was the strongest determinant factor of the clinical pregnancy rate in our model. For patients with DIE, there is some controversy as to whether removing endometriotic lesions before IVF affects pregnancy rates. Stepniewska *et al.* (2009) suggested that removal of DIE was associated with improvement of both spontaneous pregnancy and increased fertility results in ART. In a randomized trial comparing laparoscopy to open surgery for colorectal endometriosis, Daraï *et al.* (2011) reported that surgery enhanced fertility even in patients with prior IVF failure. In contrast, Mathieu d'Argent *et al.* (2010) found that the pregnancy rate in ICSI–IVF of patients with DIE involving the rectum was similar to patients with tubal or associated male infertility. A recent study showed that patients with endometriosis are a heterogeneous population including patients with poor ovarian reserve, who behave like other poor responder patients, and patients with adequate ovarian reserve with good response to ovarian stimulation exhibiting a specific alteration of the FSH receptor signalling pathway (González-Fernández *et al.*, 2011). Although several studies have reported fertility outcomes after ICSI–IVF in patients with endometriosis, to date no predictive model is available to evaluate the chance of becoming pregnant for individual patients. Furthermore, while several scoring systems to evaluate the pregnancy rate in ICSI–IVF have been recommended taking into account the patient's age, the duration of infertility, the ovarian reserve determined by the serum FSH level or the antral follicle count, none of them considered the impact of DIE as a separate entity. However, the endometriosis fertility index reduces the prognosis for patients with high revised American Fertility Society (rAFS) score >71 (implying the presence of DIE, especially in case of cul-de-sac obliteration) (Adamson and Pasta, 2010; Younis *et al.*, 2010). Therefore, our nomogram could help clinicians to refer patients either for first-line ART or a combination of surgery and ART. Finally, our nomogram provides realistic and precise information regarding ICSI–IVF success and can be used to guide couples and practitioners using clinical, imaging and biological criteria before ICSI–IVF.

The performance of the nomogram is a strong point of this study. Discrimination indicates whether the relative ranking of individual prediction is in the correct order. The high discrimination suggests that there might not be a large overlap between the distribution of probabilities in patients who became pregnant and those who did not. In our model, discrimination was 0.68 in the internal validation cohort. This can be considered acceptable, as its CI included 0.7, probably related to the relatively small sample size of the validation cohort. Unlike calibration, discrimination does not reflect the clinical significance. In this study, we also calculated average and maximal errors between predictions and observations, which give an idea of the model's performance when extrapolated to a new patient population. In our internal validation cohort, calibration was good. Using a cut-off value of 72%, the model showed an NPV of 84.6% and a false positive rate of 2.9%. This high NPV is of great importance because the purpose of the model is to better identify patients who could become pregnant after an ICSI–IVF cycle.

Some limitations of the present study have to be underlined. First, the retrospective nature of the study cannot exclude all potential biases. Secondly, no evaluation of clinical pregnancy rates according to the various anatomical locations of DIE was performed and that might be a potential bias. Thirdly, some patients had multiple ICSI–IVF cycles so that their cycles were not independent of each other. However, the aim of this model was to predict the chances of becoming pregnant for each patient, which is more useful in routine practice than the clinical pregnancy rate per cycle. In our model, the attempt number (number of ICSI–IVF cycles) was a determinant factor as it has been previously shown by Roberts *et al.* (2010) in a model to predict outcomes of embryo transfer procedures. Fourthly, our validation cohort only included 48 patients, explaining the relatively low discrimination. However, calibration, which is a major criterion to evaluate the model's performance when extrapolated to a new patient population, was good. Fifthly, external validation of predictive models is crucial before they can be exported. Most models show lower performance when they are tested outside the source population (Bleeker *et al.*, 2003). Although our model was validated in an independent internal cohort, external validation is required. Finally, we used MLR because of the limitations in clinical practice of other statistical methods, such as recursive partitioning (Rouzier *et al.*, 2009).

In the same way, Chun *et al.* (2007) also demonstrated the superiority of the logistic regression model over an artificial neural network.

In conclusion, our analysis resulted in a well-calibrated model that can predict clinical pregnancy rates in infertile women with endometriosis. If these performances are confirmed after external validation, the model could be a useful and original tool to inform patients and to adapt the ART strategy.

Authors' roles

All authors took part in the design and implementation of the study, and read and approved the final report. The corresponding author has had access to all data in this study and he had final responsibility on the decision to submit for publication. M.B. from the Department of Obstetrics and Gynecology, 'Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, Paris, France', collected and analysed all the data, performed the statistical analysis and wrote the article. A.O. collected data from patients and analysed all the data. E.M.A. collected data from patients and analysed all the data. C.T. collected data from patients. J.-M.A. analysed all the data and approved the final version of the article. C.C. collected and analysed all the data, performed the statistical analysis and wrote the article. E.D. collected data from patients, performed the statistical analysis and wrote the article.

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Conflict of interest

None declared.

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