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Original Article

Threatened preterm birth: Validation of a nomogram to predict the individual risk of very preterm delivery in a secondary care center



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ABSTRACT

Introduction: Very preterm delivery (22–32 weeks of gestation) remains a major cause of neonatal morbidity and mortality. The objective of this study was to validate a statistical model allowing to predict the risk of preterm delivery to use as a clinical decision-making tool for *in utero* transfer from a secondary to a tertiary care center.

Methods: Retrospective observational study in a secondary care center (approximately 2500 births) in Paris, France. 137 women were admitted for threatened preterm delivery between 22 and 32 weeks. Women were retrospectively allocated to the following groups based on medical decision: “transfer group” (*in utero* transfer to a tertiary care unit) and “no transfer group” (no *in utero* transfer). The risk of preterm delivery within 48 h and before 32 weeks gestation was assessed for each group using a nomogram previously validated in a tertiary care center. The primary objective of the study was to determine the accuracy of the prediction model.

Results: The discrimination and calibration of the nomogram were excellent (preterm delivery risk within 48 h, ROC AUC: 0.98, 95% CI: 0.95–1.00; probability of preterm delivery before 32 weeks gestation, ROC AUC: 0.94, 95% CI: 0.89–0.99). A threshold set at 0.16 helped minimize the risk of unnecessary *in utero* transfers with an excellent negative predictive value of 0.99.

Conclusions: We validated nomograms to predict the individual probability of preterm birth after admission in a secondary care center. Those nomograms could be helpful when making decisions regarding an *in utero* transfer to a tertiary care unit.

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Introduction

Situations involving very preterm birth require optimal care to limit morbidity whenever possible. *In utero* transfer to a tertiary level center reduces perinatal morbidity and mortality when the delivery occurs before 32 weeks gestation [1–3]. Accurate assessment of the risk of preterm birth remains a challenge in improving neonatal outcome. In clinical practice, most women treated for preterm delivery risk actually deliver at term [4]. Threatened premature delivery is defined as the combination of

painful uterine contractions and cervical modifications. Nonetheless, approximately 15% of women are hospitalized for uterine contractions only or cervical modifications only, and 5% show neither symptoms [5]. Even if both symptoms are present, the likelihood of an actual premature delivery is unknown, and most hospitalized women will not deliver before 37 weeks gestation. Threatened preterm delivery is the primary cause of hospitalization during pregnancy and the leading cause of medicalized *in utero* transfers. Accurate risk identification would help reduce unnecessary hospitalizations and *in utero* transfers for women who are actually at low risk of preterm birth.

Certain authors have tried to develop risk scores to predict premature delivery [6]. The likelihood ratios vary widely among studies, and the global accuracy of these risk scores is fairly low. Recently, Allouche et al. developed a nomogram allowing to estimate the individual risk of preterm delivery for women

Abbreviations: PROM, preterm premature rupture of membranes; ROC AUC, receiver operating characteristic curve; SD, standard deviation.

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transferred for threatened preterm delivery through perinatal care networks [7]. This score was designed to predict delivery within 48 h and before 32 weeks gestation. It includes the following elements: Preterm PROM, sonographic cervical length, gestational age at transfer, uterine contractions requiring tocolysis, multiple pregnancy, and vaginal bleeding. Its accuracy was retrospectively validated in a cohort of 169 women transferred for threatened preterm delivery to a tertiary care center but was not validated in a secondary care center. This issue is particularly relevant to avoid unnecessarily referring women to tertiary care. The discrimination and calibration of the score were good (concordance index of 0.73 and 0.72, respectively). The purpose of the present study was to validate this nomogram for use as a diagnostic tool to support clinical decision-making in a secondary care center.

Material and methods

Study population

The cohort included 137 women hospitalized for threatened premature delivery (painful and regular uterine contractions and/or cervix modifications) between 22 and 32 weeks gestation in a French secondary care center (Hôpital Tenon, Assistance Publique – Hôpitaux de Paris) between September 2009 and September 2011. Before hospitalization, an initial emergency maternal and fetal assessment was performed to evaluate the risk of preterm delivery (clinical examination, cardiotocography and ultrasound). Contractions were defined as deflections from a clear baseline, with a rounded peak lasting 40 to 120 s. For each patient, cervical length was measured by transvaginal sonography.

All women received standard care based on national guidelines [8]. There was no difference in the care given in the previous study as national guidelines had already been issued. Provided care may have included tocolysis (calcic inhibitors: nifedipine or nifedipine; oxytocin receptor antagonist: atosiban), antenatal steroids (betamethasone: two intramuscular injections of 12 mg 24 h apart) and antibiotics when preterm premature rupture of membranes (PROM) was diagnosed. PROM was defined as a fluid leak through the cervix before labor. In uncertain cases, an insulin-like growth factor binding protein-1 analysis was performed (Actim PROM®, Medix Biochemica, Kauniainen, Finland). Based on the clinical probability of delivery before 32 weeks, an *in utero* transfer to a tertiary care center was decided by the medical team. For each woman included in the study, the following data were prospectively collected: individual demographic and obstetric data (age, parity, obstetric history, and characteristics of this pregnancy), clinical characteristics at time of enrolment (vaginal bleeding,

uterine contractions requiring tocolysis, and/or preterm PROM), sonographic measurement of cervical length, delivery within 48 h of admission and delivery before 32 weeks gestation. Study exclusion criteria included prior maternal and/or fetal disease responsible for the transfer (i.e., intrauterine growth restriction, hypertension, and non-reassuring fetal heart rate). For each woman, the individual probability of preterm delivery within 48 h and before 32 weeks gestation was calculated using the previously published nomogram available at <http://www.perinatology.com/calculators/TRANSFER.htm> [7]. Preterm PROM, sonographic cervical length, gestational age at transfer, uterine contractions requiring tocolysis, multiple pregnancy, and vaginal bleeding are associated with the obstetric outcome and are used in the calculation of the probability of preterm delivery. *In utero* transfers were not performed according to calculated risks. Risk calculation was retrospectively performed. *In utero* transfers were requested by clinicians based on clinical and ultrasound features. Women were retrospectively allocated to the following groups according to the medical decision: “transfer group” (*in utero* transfer to a tertiary care unit) and “no transfer group” (no *in utero* transfer). The primary aim was to validate previously published nomograms to predict the individual probability of preterm birth before transfer for threatened preterm delivery from a secondary to a tertiary care unit. The secondary endpoint was to set the threshold for deciding whether an *in utero* transfer is needed.

Statistical analysis

All data were entered into a prospectively collected database. Nonparametric Mann-Whitney and Fisher’s exact tests were used to compare quantitative and qualitative data, respectively; $p < .05$ was considered to be significant.

The model performance was quantified as previously described with respect to discrimination and calibration. The discrimination (i.e., whether the relative ranking of individual predictions is in the correct order) was quantified using the area under the receiver operating characteristic curve (ROC AUC) or the concordance index, which is similar to the ROC AUC but is appropriate for censored data. The concordance index is the probability that given two randomly selected patients, the patient with the worse outcome prediction will in fact have a worse outcome. The concordance index ranges from 0 to 1, with 1 indicating perfect concordance, 0.5 indicating no better concordance than chance, and 0 indicating perfect discordance. We used the bootstrapping method (200 repetitions) to obtain relatively unbiased estimates. The calibration (i.e., alignment between observed outcome frequencies and predicted probabilities) was studied with

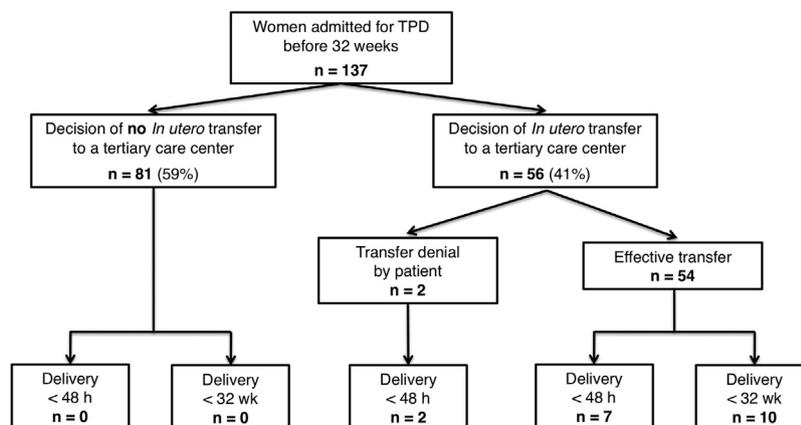


Fig. 1. Flow chart. TPD, threatened preterm delivery.

graphical representations of the relationship between the observed outcome frequencies and the predicted probabilities (calibration curves). These curves present the grouped proportions vs. the average predicted probability in groups defined by quantiles.

To determine the best preterm risk threshold (minimization of false-negative and false-positive rates), two statistical tools were used: Youden's index and MinROCDist. Youden's index is the threshold that maximizes the sum of sensitivity and specificity ($Y = Se + Sp - 1$); it minimizes the average error rate for positive observations and the error rate for negative observations. MinROCDist is a cut-off that minimizes the distance between the ROC plot and the upper left corner of the unit square.

To calculate the power of the test (necessary to estimate sample size effect), we considered that individual predictions of delivery rates were constant as the null hypothesis. Based on our sample size, we estimated a proportion of 0.05 delivery in the no transfer group and 0.2 in the transfer group (based on observed data): power = .78.

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

Results

Study population

Between September 2009 and September 2011, 137 eligible women were enrolled in the study. An *in utero* transfer to a tertiary level care unit was decided upon for 56 women (41%) (Fig. 1). Two women declined to be transferred and delivered within 48 h of admission. About half of the women were nulliparous, and most of the pregnancies were singletons (Table 1). As expected, twin pregnancies were more frequently included in the “transfer group” (11 (20%) in the “transfer group” versus 3 (4%) in the “no transfer group”, $p < .005$). Women with a history of late miscarriage and/or prophylactic cerclage were more likely to be transferred, whereas a history of previous spontaneous birth before 32 weeks did not seem to impact the decision regarding *in utero* transfer. At admission, there were no statistical differences between the

groups in terms of uterine contractions, preterm PROM or vaginal bleeding. Cervical length at time of admission was significantly shorter in the “transfer group” (16.1 mm \pm 12.0) than in the “no transfer group” (25.5 mm \pm 8.1; $p < .001$).

Prediction of the probability of preterm delivery within 48 h

None of the women in the “no transfer group” delivered within 48 h of admission (Fig. 1 and Table 2A), whereas nine (16%) women in the “transfer group” delivered within 48 h. None of the women included in the study delivered prematurely for iatrogenic reasons. According to the nomogram, the average likelihood estimation of very preterm delivery within 48 h was 10% in the whole population, 19% in the “transfer group” versus 5% ($p < .0001$) in the “no transfer group” (Table 2B). When applied to our secondary care unit cohort, the prediction model had a ROC AUC of 0.98 (95% CI: 0.95–1.00) (Fig. 2A). The calibration was assessed graphically using the unreliability index (Fig. 2B). There was a slight difference between the observed and predicted probabilities ($p = .03$); we observed an overestimation of the risk of preterm delivery within 48 h in the whole cohort, but the calibration was excellent for the transferred women (Supplemental Fig. A).

Prediction of the probability of preterm delivery before 32 weeks gestation

None of the women in the “no transfer group” delivered before 32 weeks gestation after admission (Fig. 1 and Table 2A), whereas 12 (22%) women in the “transfer group” delivered before 32 weeks. According to the nomogram, the average likelihood estimation of preterm delivery before 32 weeks was 28% in the whole population, 41% in the “transfer group” versus 19% ($p < .0001$) in the “no transfer group” (Table 2B).

When applied to our secondary care unit cohort, the prediction model had a ROC AUC of 0.94 (95% CI: 0.89–0.99) (Fig. 3A). There was a significant difference between the observed and predicted probabilities ($p < .001$); we also noticed an overestimation of the risk of preterm delivery before 32 weeks in the whole cohort (Fig. 3B), but the calibration was excellent for the transferred women (Supplemental Fig. B).

Table 1
Characteristics of the women in the panel and their pregnancies.

Characteristics	Whole population (n = 137)	Transfer group (n = 56)	No transfer group (n = 81)	p-value
Age, mean \pm SD	29.9 \pm 5.9	29.0 \pm 5.6	30.6 \pm 6.1	NS
Gestational age at inclusion, mean in wk \pm SD	28.4 \pm 2.8	27.3 \pm 2.8	29.2 \pm 2.5	< .0001
< 24 wk, n (%)	10 (7)	6 (11)	4 (5)	
24–28 wk, n (%)	44 (32)	23 (41)	21 (26)	< .05
28–32 wk, n (%)	83 (61)	27 (48)	56 (69)	
Nulliparous, n (%)	64 (47)	25 (44)	39 (48)	NS
Singleton/twins, n (%)	123 (90) / 14 (10)	45 (80) / 11 (20)	78 (96) / 3 (4)	< .005
Previous spontaneous birth <32 wk, n (%)	12 (9)	5 (9)	7 (9)	NS
Previous late miscarriage between 14 and 24 wk, n (%)	9 (7)	8 (14)	1 (1)	< .05
Prophylactic cerclage, n (%)	11 (8)	8 (9)	3 (37)	< .05
<i>Clinical and ultrasound features at admission</i>				
Uterine contractions, n (%)	111 (81)	49 (87)	62 (76)	NS
Preterm PROM, n (%)	11 (8)	7 (13)	4 (5)	NS
Vaginal bleeding, n (%)	3 (2)	2 (3)	1 (3)	NS
Cervical length, mean in mm \pm SD	21.6 \pm 10.9	16.1 \pm 12.0	25.5 \pm 8.1	< .0001
<15 mm, n (%)	28 (20)	24 (43)	4 (5)	
<25 mm, n (%)	52 (38)	8 (14)	44 (54)	< .001
\geq 25 mm, n (%)	57 (42)	24 (43)	33 (41)	

Nonparametric Mann-Whitney and Fisher's exact tests were used to compare the quantitative and qualitative data between “transfer group” and “no transfer group”, respectively. NS, nonsignificant; PROM, premature rupture of membranes; SD, standard deviation.

Table 2

Actual delivery and risk of preterm delivery according to the nomograms, within 48 h and before 32 weeks gestation.

A						
Delivery within 48 hours and before 32 weeks gestation after admission according to each group						
	Delivery <48 h		p-value	Delivery <32 wk		p-value
	Yes	No		Yes	No	
Whole population, n (%)	9 (7)	128 (93)	< .001	12 (9)	125 (91)	< .001
Transfer group, n (%)	9 (16)	47 (84)		12 (22)	44 (78)	
No transfer group, n (%)	0 (0)	81 (100)		0 (0)	81 (100)	

B			
Average likelihood estimations according to nomograms for preterm deliveries within 48 hours and before 32 weeks			
	Delivery <48 h		Delivery <32 wk
Whole population	0.10		0.28
Transfer group	0.19		0.41
No transfer group	0.05		0.19
p-value	< .0001		< .0001

Nonparametric Mann-Whitney and Fisher's exact tests were used to compare the quantitative and qualitative data between "transfer group" and "no transfer group", respectively. h, hours; wk, weeks.

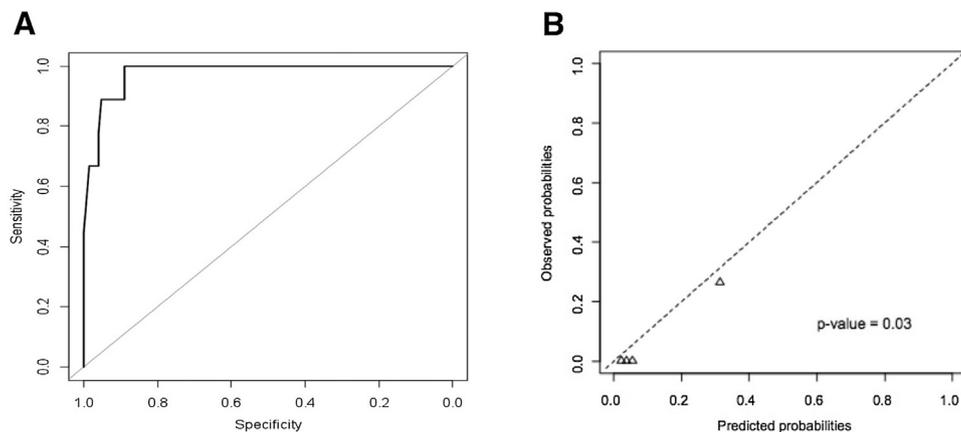


Fig. 2. Accuracy and calibration of the prediction model for delivery within 48 h of admission. **A.** ROC curve of the nomogram for the prediction of premature birth within 48 h. Concordance index: 0.98 (95% CI: 0.95–1). **B.** Calibration of the model. The x-axis represents the probability of delivery within 48 h after transfer calculated using the nomogram, and the y-axis represents the actual rate of delivery within 48 h. The dashed line represents the performance of an ideal nomogram. The predicted and observed rates of delivery within 48 h are plotted as the grouped observations and logistic calibration.

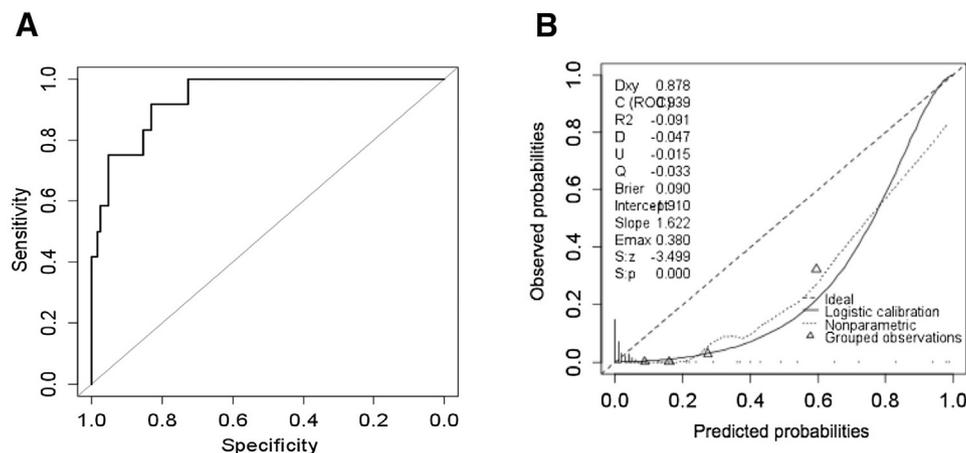


Fig. 3. Accuracy and calibration of the prediction model for delivery before 32 weeks after admission. **A.** ROC curve of the nomogram for the prediction of premature birth before 32 weeks. Concordance index: 0.94 (95% CI: 0.89–0.99). **B.** Calibration of the model. The x-axis represents the probability of delivery before 32 weeks after transfer calculated using the nomogram, and the y-axis represents the actual rate of delivery before 32 weeks. The dashed line represents the performance of an ideal nomogram. The predicted and observed rates of delivery before 32 weeks are plotted as the grouped observations and logistic calibration.

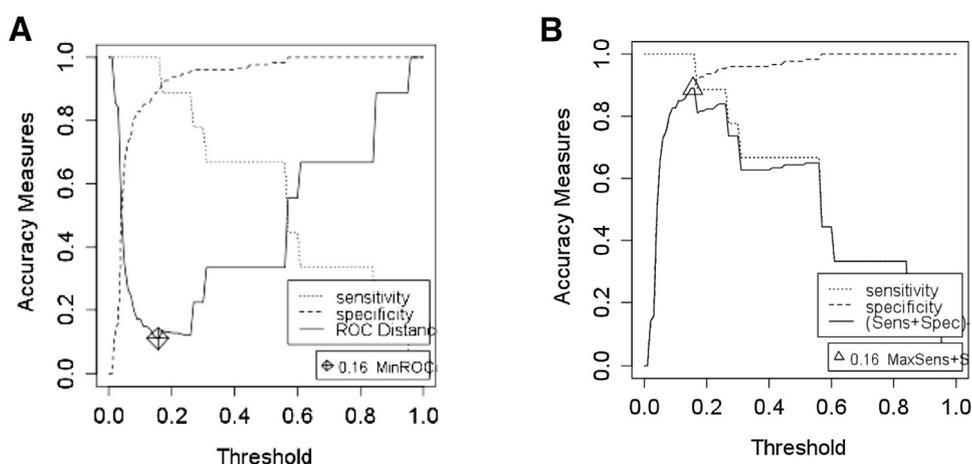


Fig. 4. Preterm birth risk within 48 h: optimal threshold determination. To determine the best preterm risk threshold (minimization of false-negative and false-positive rates), two statistical tools were used: MinROCDist and Youden's index. **A.** MinROCDist is the cut-off that minimizes the distance between the ROC plot and the upper left corner of the unit square. **B.** Youden's index is the threshold that maximizes the sum of sensitivity and specificity ($Y = Se + Sp - 1$); this index minimizes the mean of the error rate for positive observations and the error rate for negative observations.

Preterm birth risk within 48 h: optimal threshold determination

We determined the optimal threshold for the risk of preterm delivery within 48 h because of its particular relevance in emergency obstetrical care. According to the MinROCDist (Fig. 4A) and Youden's index (Fig. 4B) calculations, the optimal threshold for considering an *in utero* transfer is 0.16 when looking at the risk of preterm delivery within 48 h. With a threshold of 0.16, the sensitivity and specificity were 0.89 (95% CI: 0.52–0.98) and 0.90 (95% CI: 0.83–0.94), respectively (Fig. 5).

Discussion

Very preterm birth is the main factor associated with perinatal mortality and severe morbidity, accounting for more than 50% of perinatal deaths [9–12]. The identification of women at risk for very preterm delivery among those presenting symptoms of preterm labor relies on obstetric history and an assessment of clinical and ultrasound features (uterine contractions, cervical length, and preterm PROM) [10]. We observed an excellent ROC AUC of 0.98 (95% CI: 0.95–1.00) for the 48-hour risk nomogram. It was previously assessed in a tertiary care center, and we performed

an independent validation of this prediction model based on the combination of multiple routine clinical and sonographic variables with excellent discrimination. We noticed a higher ROC AUC in our study than in previously published cohort: 0.73 (95% CI: 0.66–0.80) [7]. It could be mostly explained by lower prevalence rates of preterm births in secondary care centers than in tertiary care centers. Accordingly, it improves negative predictive value and thus ROC AUC.

In our study, *in utero* transfers were not performed based on calculated risks. Preterm PROM is a major argument in favour of a decision of *in utero* transfer to a tertiary care center. This main risk factor of preterm birth is an integral part of both nomograms with a relative weight of approximately 20 percent of the overall risk [7]. Therefore, its impact has necessarily been taken into account regardless of preterm PROM rate in the validation set.

Correct prediction of very preterm birth would be useful if it enabled interventions to reduce mortality and morbidity associated with preterm birth [13]. Nevertheless, women may be hospitalized and receive unnecessary treatments. We observed that most admitted, but not transferred, women did not deliver during the very preterm period (81/137), but the positive predictive value (PPV) was low. Conversely, other women may

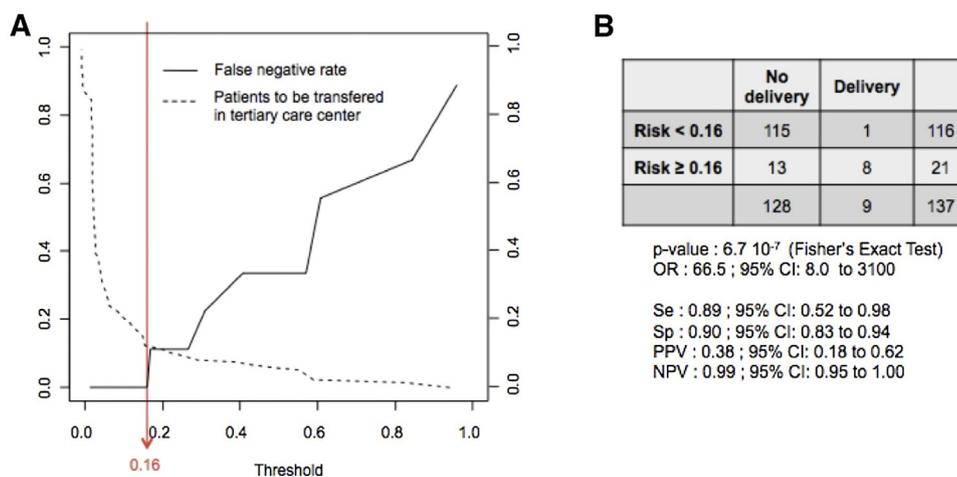


Fig. 5. Accuracy of the prediction model of delivery within 48 h after admission according to the threshold. **A.** False-negative rate (bold line) of the prediction model of delivery when modifying the threshold. The percentage of women who require a transfer are mentioned when modifying the threshold (dashed line). The threshold of 0.16 was calculated according to Youden's index and MinROCDist (red vertical bar). **B.** Accuracy of the nomogram with a threshold of 0.16 according to our secondary care center cohort. NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

receive tocolytic therapy rather late, and the decision to conduct an *in utero* transfer may be made too late (risk of outborn birth). The assessment of women at risk for very preterm labor must be accurate and objective. Our study demonstrated the relevance and ease of use of a nomogram to predict the individual risk of very preterm delivery within 48 h after admission for threatened preterm delivery in a secondary care unit before 32 weeks of gestation. As expected, predicting a delivery within 48 h was more accurate than predicting delivery before 32 weeks of gestation because it is a more immediate event. Indeed, we noticed excellent discrimination and correct calibration of this model based on routine clinical variables and cervical ultrasonography, thereby offering an independent validation of this previously published tool. We decided to promote this prediction model based on universally utilized and affordable criteria to simplify clinical decision-making. Some of the weaknesses in our findings relate directly to the retrospective nature of the study; nevertheless, we emphasize the comprehensiveness of the reported data.

The selection of a preterm risk threshold remains crucial to avoid providing unnecessary care. Retrospectively, the threshold of our cohort was implicitly established at 0.05. A threshold of 0.16 would help minimize the risk of outborn deliveries with an excellent negative predictive value (NPV) of 0.99 (21 *in utero* transfers for eight preterm deliveries and 116 decisions not to transfer for one outborn preterm delivery within 48 h). The actual benefits of risk scoring for the prevention of preterm birth are unknown [13]. Although many risk scores have been published over the past 30 years, no randomized controlled interventional trials have been conducted. Indeed, we must determine the optimal threshold to avoid unnecessary transfers of women who will not delivery prematurely to a tertiary unit.

We highlight the difficulty to establish an accurate diagnosis of threatened preterm delivery (44/56 women of the “transfer group” delivered after 32 weeks and 23/56 delivered after 37 weeks). In our cohort, a cervical length of less than 25 mm has been observed in more than 60% of women. In symptomatic patients, cervical length is used in routine to predict the risk of preterm delivery. Boots and colleagues provided a meta-analysis which evaluated the diagnostic accuracy of different morphological tests or biomarkers for the prediction of preterm delivery. Cervical length diagnostic accuracy had been evaluated: ROC AUC for the prediction of preterm delivery within 48 h in symptomatic patients was 0.90 (95% CI 0.88–0.93) when used alone [14]. Although shortened cervical length is a major marker of preterm delivery in symptomatic women, one could argue that the fetal fibronectin test has not been implemented in combination with cervical length in evaluating preterm delivery risk [15]. Indeed, the sensitivity of the fetal fibronectin test is higher when combined with cervical sonography [16,17]. Recently, Kuhrt and colleagues established a predictive model that included quantitative fFN and history of preterm birth and/or preterm PROM with an accurate risk calculation in both symptomatic and asymptomatic women [18]. In a similar way, two modified prediction models based on Allouche and colleagues’ work were published [19]. The authors pointed out the great accuracy of fetal fibronectin test, however the 48 h modified prediction model did not take it into account. There was a high representation of admitted women with a gestational age of less than 24 weeks (24% of the cohort). Fetal fibronectin detection before 24 weeks must be use with caution because of its moderate value in predicting very preterm spontaneous birth: it could be partially explained by the physiological presence of fFN in cervicovaginal fluid in patients at less than 24 weeks [20].

Nomograms facilitate decision-making, but this prediction score should be implemented after a cost-effectiveness analysis is performed to determine whether the routine assessment of the risk of premature birth in cases of threatened preterm labor is a cost-

effective strategy [21,22]. Werner and colleagues conducted an analysis among asymptomatic women; routine cervical length measurements were performed with or without daily vaginal progesterone supplementation [23]. The authors demonstrated that a screening program with appropriate interventions to reduce preterm birth would be cost-effective and cost-saving. These data were consistent with another previously published study [24]. Nevertheless, no one has evaluated the cost-effectiveness of this strategy in symptomatic women or of the use of a screening tool for determining premature birth risk and its impact on the *in utero* transfer decision. A well-designed prospective randomized controlled clinical trial is needed to confirm these risk score results, including an evaluation of maternal well-being and a cost-effective analysis.

Ethics approval and consent to participate

This study was approved by the CNIL (Commission Nationale de l’Informatique et des Libertés, French law no. 78–17). All data were de-identified to ensure patient privacy and confidentiality. Oral informed consents have been obtained from the participants. According to the French law, written informed consent is not required for this observational retrospective study.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

Funding

None.

Authors' contributions

AJV analyzed the data and wrote the manuscript. BM collected and analyzed the data. MB, ED and FR participated in the analysis of the data. RR conceived the study, analyzed the data and wrote the manuscript. All authors have seen and approved the final version. AV & BM contributed equally to this work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jogoh.2019.04.004>.

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