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Original Article

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Marion Gioan [a], Florence Fenollar [b], Anderson Loundou [c], Jean-Pierre Menard [d], Julie Blanc [e], Claude D'Ercole [e,f], Florence Bretelle [e,f,*]

[a] CHG Sainte-Musse, 54, rue Henri-Sainte-Claire-Deville, 83100 Toulon, France
[b] Unité de recherche sur les maladies infectieuses tropicales et emergentes, UM63, CNRS 7278, IRD 198, INSERM 1095, 13000 Marseille, France
[c] Medical Evaluation, Department of Public Health, Assistance publique–hôpitaux de Marseille, AMU, Aix-Marseille Université, 13000 Marseille France
[d] Conseil départemental du Val-de-Marne, 94000 Créteil, France
[e] Department of Gynaecology and Obstetrics, Gynepole, AP–HM, Assistance publique–hôpitaux de Marseille, 13000 Marseille, France
[f] AMU, Aix-Marseille Université, 13000 Marseille, France

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ABSTRACT

Objective. – This study aimed to develop a new tool for personalised preterm birth risk evaluation in high-risk population.
Study design. – 813 high-risk asymptomatic pregnant women included in a French multicentric prospective study were analysed. Clinical and paraclinical variables, including screening for bacterial vaginosis with molecular biology, cervical length, have been used to create the nomogram, based on the logistic regression model. The validity was checked by bootstrap. A downloadable calculator was build.
Results. – Nine risk factors were included in this model: history of late miscarriage and/or preterm delivery, active smoking, ultrasound cervical length, term of pregnancy at screening, bacterial vaginosis, premature rupture of membranes, daily travel more than 30 min. Discrimination and calibration of the nomogram revealed good predictive abilities. The area under the receiver operating characteristic curve was 0.77 (95% CI; 0.72–0.81). The mean absolute error was 0.018, which showed proper calibration. The optimal risk threshold was 23.2% with a sensitivity of 74%, a specificity of 72.7% and a predictive negative value of 90.6%.
Conclusion. – The nomogram can help to better define individual preterm birth risk in high-risk pregnancies.

Introduction

Preterm Birth (PB) remains the cause of neonatal morbidity and mortality in developed countries with up to 9% of pregnancies word wile [1]. In Europe PB occurs in 4.1 to 8.2% of birth leading to maternal prolong hospitalisations and treatments especially in high risk pregnancies [2,3]. Based on the definition, an asymptomatic pregnant woman with a history of PB or late miscarriage is considered at high risk for PB. Ultrasonographic cervical measurement is the standard gold to evaluate this risk. The risk depends on cervical length and gestational age at measurement [4]. The addition of risk factor for the evaluation of PB risk could be a clue to improve the prediction of PB risk. For example Bacterial vaginosis (BV) is a risk factor for obstetrical complications [5,6]. The detection by molecular biology of microorganisms present in BV is a new diagnostic approach [7,8]. Ménard et al showed that the time to delivery was shorter when high atopobium vaginal load was detected in a high risk population [8,9]. No reliable predictive method exists today to define the risk of PB in high-risk pregnancies [10].

The nomogram is the graphic representation of the probability for each patient of an event. With this model, the risk calculation is simple, reproducible and personalised. Two recent studies proposed an assessment of PB risk in high-risk populations [11,12]. Unfortunately, their calculations did not incorporate most of the variables recognised as risk factors for PB, such as vaginal swab results, history of adverse event or maternal smoking. Our study aim was to develop a new tool to evaluate individual risk for PB in a high-risk population.

* Corresponding author. Unité de recherche sur les maladies infectieuses tropicales et emergentes, UM63, CNRS 7278, IRD 198, INSERM 1095, 13000 Marseille, France
E-mail addresses: melkorsa@gmail.com (M. Gioan), florence.bretelle@ap-hm.fr (F. Bretelle).

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Materials and methods

Target population

The established nomogram has been created from the database of a prospective multicentric French cohort [13]. Pregnant women, who are 14 to 34 weeks (wks) pregnant, admitted for prenatal care in eight French teaching hospitals (among them two level II and six level III, all were public hospital except one), wishing to participate in the study, were eligible.

Taking into account a 30% proportion of preterm births before 37 weeks in our high risk population, a sample size of 690 women should show a hazard ratio (HR) of approximately 3.3 for *Atopobium vaginae* at a power at 80. With lost to follow-up patients and missing data (estimated at 20%) into account, 820 women is required.

Inclusion criteria

The patients included were older than 18 years and at risk for PB. This risk was defined as the existence of a short cervix (a cervical length <25 mm measured by transvaginal ultrasound) and/or an obstetric history: history of preterm birth and/or late miscarriage (spontaneous expulsion of a pregnancy ≥14 and <22 wks).

The exclusion criteria were: multiple pregnancies, treated hypertension, foetal malformation, antiphospholipid syndrome, diabetes, pre-eclampsia, renal disease, any auto-immune disease, or an antibiotic treatment in the past 7 days.

A complete medical examination and interrogation collected the demographic data, medical history (age, parity, body mass index, smoking during pregnancy, obstetric history, and current pregnancy data) and the clinical characteristics of each patient (uterine contractions, clinical signs of BV or premature rupture of membranes).

Vaginal sample and ultrasound measurement of the cervical length were performed. Gestational age was determined from the date of the last menstrual period or on the first trimester ultrasound in case of a one-week lag. The daily travel time data was collected and divided into two groups: more or less than 30 min. Obstetric and neonatal outcomes were collected in the postpartum period through consultation of medical files.

Bacteriological analysis

The bacteriological analysis was performed with self-collected vaginal swabs. Menard et al. [14] demonstrated the validity and reliability of this method versus practitioner-collected swab for molecular quantification. Each vaginal sample received a molecular biology analysis based on quantitative PCR. The results were blinded for the medical team of obstetricians. The organisms targeted by quantitative PCR and selected in our study were *A. vaginae* and *Gardnerella vaginalis*. Molecular quantification of *A. vaginae* $\geq 10^8$ copies/ml and/or *G. vaginalis* $\geq 10^9$ copies/ml has been described as common in women with BV flora [8]. The trial was registered at ClinicalTrials.gov (identifier NCT00484653), and funded by the national hospital clinical research program (Programme de Recherche Clinique, number 2007-A00069-44). "Le Comité de Protection des Personnes Sud Méditerranée V" approved the project (number 07.019). Analysis method was previously reported [13].

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics version 20 software. The association between the variables selected in the preliminary study and the risk for PB was tested with univariate and multivariate logistic regression analyses. Logistic model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test to evaluate the discrepancy between observed and expected values. Odds ratios were reported with 95% confidence interval (CI 95%). Qualitative variables were presented in the form of enrollment counts and percentages. Quantitative variables were expressed as mean ± standard deviation. The retained and integrated variables were the term (expressed as weeks of gestation (wks)), history of preterm and late miscarriage, premature rupture of membranes, smoking, daily travel time, BV diagnosed with molecular biology, sonographic measurement of cervical length, and the combination of history of preterm birth and cervical length <25 mm. Discrimination, calibration, and nomogram were performed using the "rms" library of the R software (http://www.R-project.org) [15]. The predictive model was internally validated for calibration with bootstrap resampling. This compares predicted PB and actual PB probabilities. The calibration was studied with a χ^2-test with two degrees of freedom. Discrimination was examined using the area under the receiver operating characteristic (ROC) curve (AUC), graphic representation of the false-positive rate based on the sensitivity of each model value. AUC > 0.8 represents an excellent discriminating power, and is good when comprised between 0.7 and 0.8 [16]. An AUC of 0.5 is random. The AUC is associated with 95% confidence interval (CI). The optimal threshold value for the risk of PB is the point on the ROC curve that is furthest from the diagonal and that represents the zero contribution test [17]. All the tests were two-sided. The statistical significance was defined as $P < .05$.

Results

Study

Between July 2007 and April 2012, 813 patients were included. PCR scores were performed on 764 vaginal samples. Data results were reported elsewhere [13]. In brief, the mean maternal age was 29.4 years (±5.6) and the percentage of multiparous patients was 17.5%. Mean gestational age of pregnancies at inclusion was 26.3 (±5.1) wks. A total of 220 patients (28.8%) gave birth before 37 wks, a total of 142 patients had an obstetric history of PB or late miscarriage. Among them, 122 women (86%) had a short cervix. A cervix length < 25 mm was observed in 622 patients without adverse event history. Based on molecular definition of BV, 70 (9.2%) patients were BV carriers.

Among women who delivered prematurely, 24 (10.9%) had BV versus 46 (8.5%) in the group where women delivered at term.

Predictive model of preterm birth risk in high-risk population

The results of the univariate and multivariate analysis are listed in Table 1. A multivariate logistic regression analysis demonstrated significant and independent associations between delivery before

Table 1
Univariate and multivariate analysis of Preterm birth risk factors. OR, odds ratio; aOR, adjusted OR; CI, confidence interval; PB, preterm birth; PROM, premature rupture of membranes.

Variables	OR [CI 95%]	*P*	aOR [CI 95%]	*P*
History of PB	1.5 [1–2]	0.05*	3.6 [1.2–11]	0.019*
History of late miscarriage	1.2 [0.7–1.9]	0.5	1.6 [0.5–5]	0.41
Gestational age	0.9 [0.9–0.96]	<.001*	0.9 [0.8–0.9]	0.002*
Bacterial vaginosis	1.3 [0.8–2.2]	0.3	1.6 [0.6–4]	0.33
Smoking during pregnancy	1.2 [0.8–1.7]	0.3	1.5 [0.8–2.9]	0.23
Sonographic cervical length	0.9 [0.9–0.96]	<.001*	0.9 [0.8–0.9]	0.001*
History of PB + cervical length <25 mm	1.9 [1.2–2.8]	0.002*	0.4 [0.1–1.4]	0.16
Day travel time > 30 min	1.4 [1.00–1.9]	0.05*	2.6 [1.4–4.9]	0.002*
PROM	2.3 [1.3–4.1]	0.002*	3.6 [1.7–7.5]	0.001*

* Significant variables.

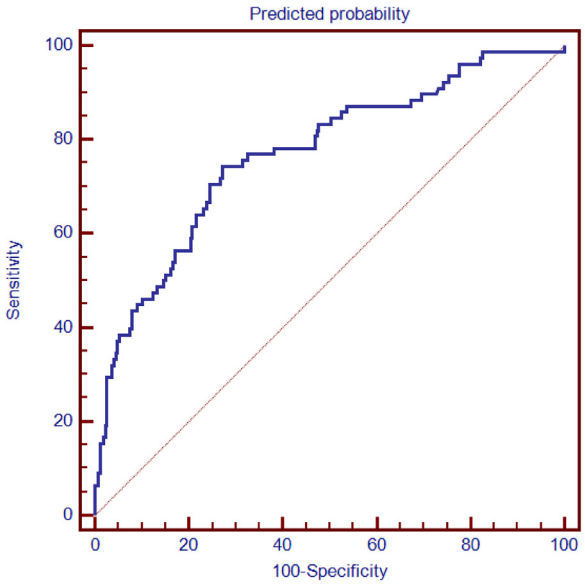

Fig. 1. Receiver Operating Characteristic curve: predictive model discrimination.

37 wks and sonographic cervical length, history of preterm birth, early gestational age at inclusion, premature rupture of membranes (PROM), and superior daily travel time of 30 min. History of late miscarriage, combination of history of preterm birth and cervical length <25 mm, smoking during pregnancy and molecular diagnosis of BV were not associated with PB in our cohort, although these variables were significantly associated with a PB in a univariate analysis in the preliminary study. The literature recognizes these variables as risk factors for PB. We have chosen to integrate these elements into the calculator. The AUC after bootstrap for the validation set was 0.77 (95% CI; 0.72–0.81) (Fig. 1).

We used 500 bootstrap resamples for internal validation of accuracy estimates and to reduce overfit bias. The mean absolute error was 0.018. The maximum error was 0.0682. The mean squared error was 0.00051. It represents the quality of measure of an estimator, as a result close to zero shows good calibration. We have therefore developed a nomogram to predict individual preterm birth risk in asymptomatic high-risk population (Fig. 2).

The optimal predictive value of the PB risk in high-risk populations has been determined from the ROC curve. The optimal probability threshold is 23.2% which offers different thresholds depending on statistical variables (Table 2). Prioritizing sensitivity to determine the threshold to use seems essential. Its use in clinical practice will allow minimising the rate of false-negative results.

Discussion

The present study developed a new predictive model for assessing the individual risk of PB in a high-risk population. Our nomogram evaluates a probability score based on the main well known risk factors of spontaneous PB and includes newly other risk factors. In our study according to literature [18], cervical length was one of the strongest risk factor for PB with the history of

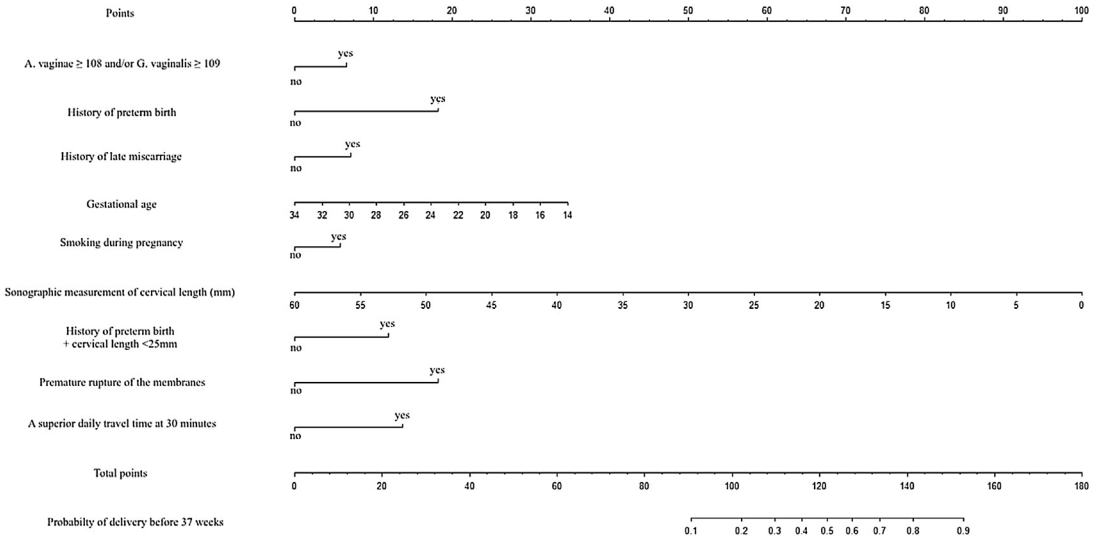

Fig. 2. Nomogram.

Table 2
Prediction of the risk of individual preterm birth in high-risk population. Se, sensitivity; Sp, specificity; LHR+, positive likelihood ratio; LHR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

PB rate (%) [95% CI]	8	15	23,2	30	55	74
Se	100 (95.4–100)	82 (71.7–89.8)	74 (63.2–83.6)	56 (44.7–67.6)	23 (14.3–34)	6.4 (2–14)
Sp	0 (0.0–1.4)	52.3 (46–58.4)	72.7 (67–78)	80.7 (75.4–85.3)	97.3 (94.6–99)	100 (98.6–100)
LHR+	1 (1.0–1.0)	1.7 (1.5–2)	2.7 (2.2–3.5)	2.92 (2.1–4.0)	8.7 (3.8–20.1)	NA
LHR−	NA	0.34 (0.2–0.6)	0.35 (0.2–0.5)	0.54 (0.4–0.7)	0.79 (0.7–0.9)	0.94 (0.9–1.0)
PPV	22.8 (18.7–27.5)	33.5 (27.2–40.5)	44.6 (36.3–53.12)	45.8 (36.2–55.8)	72 (52.4–85.7)	100 (56.5–100)
NPV	NA	90.7 (85–94.4)	90.6 (85.8–93.8)	86.2 (81.31–89.9)	81 (76.4–85)	78.3 (73.6–82.4)

previous PB, PROM and long daily travel time. Some of the latest variables have never been used in a nomogram before. For example our results show an independent association between daily travel time and the risk of PB and was included in the model. Active smoking was also included in the model, even if non-significant in our results because of its previously was reported an association with PB (OR: 1.27, 95% CI: 1.21–1.33) [19]. Previous PB was a strong and independent risk factor for PB in our study as previously reported in a meta-analysis with an absolute recurrence risk of 20.2% (95% CI: 19.9–20.6) [2]. PROM was an independent and strong risk factor for PB in our study and but had previously been included in a risk-calculating nomogram [11,12].

In our model bacterial vaginosis was included even if it did not increase the risk for PB after multivariate analysis. The association between BV and PB has been previously reported, with a shorter time to delivery, reason why it was included in the model. A pregnant woman carrying BV has twice the risk of giving birth prematurely (OR: 2.16, 95% CI: 1.56–3.00) [20], especially if screening was performed early during pregnancy [6]. In this situation the risk of late miscarriage is six times higher (OR: 6.32; 95% CI: 3.65–10.94) [20]. Nevertheless the screening and treatment of asymptomatic BV in low-risk patients are not recommended and remain controversial for high-risk patients [21,22]. Because of heterogeneous BV definition, treatment, gestational age at screening. While waiting for the results of an on-going study [23], BV screening and treatment are recommended for the sub-population of asymptomatic patients with a history of adverse events in a mother–foetal infectious context [24].

A reliable screening tool should help for optimal management. The better identification of high-risk PB patients by using a predictive tool could limit medical costs. This could help also to decide the time of corticosteroids in order to avoid too early or repeated treatments that could be inefficient or dangerous for children [25].

Our predictive tool has been created based on a multicentric study performed with a large French cohort of patients. It could therefore be reproducible in high risk population. Until now, the only recommended monitoring tool was the length of the cervix or the foetal fibronectin between 16 and 22 wks [26,27]. Our model proposes to personalise the calculation of PB risk with additional risk factors.

Our study has some limits. To begin the use of molecular biology cannot be set up everywhere at the moment. Our model has not been validated on an independent population. We have used the re-sampling by bootstrap technique to counter the lack of external validity. The internal validity of our nomogram is improved by a high number of repetitions. Unfortunately, a tool is not applicable to patients at risk of preterm delivery for multiple pregnancy or uterine malformation. The low-risk population and induced labour are also not concerned. Other risk factors as the number of previous PBs, particularly in case of successive events, and the gestational of delivery of the previous PB could have been also included in order to improve accuracy of the nomogram [28].

Conclusion

An innovative calculator tool was developed in order to better define the individual risk of PB in high risk pregnancies. The accuracy of our predictive tool for the risk of PB should be further evaluated in a prospective study.

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