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Prediction of spontaneous preterm delivery in the first trimester of pregnancy

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ABSTRACT

Objective: To develop a model for predicting premature delivery before 37 weeks' gestation based on maternal factors, obstetric history and biomarkers in the first trimester of pregnancy.
Study design: Cohort study based on data collected prospectively between 1 January 2000 and 30 November 2011. Multivariate logistic regression was used to construct a model of the risk of premature delivery.
Results: 31,834 pregnancies were included, of which 1188 cases were spontaneous premature deliveries before 37 weeks (3.7%). We built a predictive model based on maternal age, body mass index, smoking status and previous obstetric history. This could identify 23.3% of premature deliveries in our study population, with a false positive rate of 10%. In the group of patients who had already had at least one pregnancy at or beyond 16 weeks, the detection level increased to 29.7%. The positive predictive value was 7.4 and 7.3% respectively, while negative predictive value was 97.2 and 97.9%.
Conclusions: Predicting preterm delivery on the basis of maternal characteristics and obstetric history needs to be further improved. PAPP-A levels and ultrasonographic measurement of cervical length could not be integrated in the model but require further investigations.
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1. Introduction

Prematurity is the chief cause of neonatal morbidity and mortality [1,2] and appears to be slightly on the rise in Europe and the United States [3,4]. A distinction must be made between spontaneous preterm birth (spontaneous onset of labour and premature rupture of the membranes) and induced preterm birth (because of small for gestational age and/or pre-eclampsia) [5]. Spontaneous preterm birth accounts for approximately two-thirds of all cases of prematurity [6]. Identification of patients at risk of spontaneous preterm delivery is an important issue since preventive treatments exist which have proven to be effective in selected cases: progesterone [7–9] and cervical cerclage [10,11].

Development of a tool enabling early identification in the first trimester of pregnancy of patients at risk of preterm delivery would therefore be of great utility since these patients could be offered a personalised monitoring and management programme adapted to their level of risk. This is the direction taken by Nicolaides et al., who proposed a method for calculating the risk of spontaneous preterm delivery before 34 weeks based on various predictive factors already identifiable in the first trimester [12]. This tool reportedly enabled between 18.4 and 38.2% of premature deliveries to be detected, depending on whether the target patient population was nulliparous or primiparous, for a 10% false positive rate.

The principal aim of our study was to develop a predictive model for spontaneous preterm birth before 37 weeks gestation in singleton pregnancies in a French population patient group with characteristics different from the cohort of British patients in Nicolaides' study. The secondary objective was to evaluate the utility of combining this risk estimation in the first trimester with the observation of threatened preterm delivery in the second or third trimesters.

2. Materials and methods

2.1. Patient population

This was a cohort study based on data collected prospectively in the electronic medical records at the Centre Médico-Chirugical et

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Obstétrical (CMCO), Schiltigheim, France. Patients included had a singleton pregnancy, an antenatal consultation before 14 weeks, and a delivery after 24 weeks. We excluded pregnancies with imprecise dates, fetal deaths, medical terminations of pregnancy and cases of induced preterm delivery before 37 weeks. The study examined data collated between 1 January 2000 and 30 November 2011. Assays of maternal serum PAPP-A and free β-hCG were available only after 2004. The main outcome was the occurrence or non-occurrence of spontaneous delivery before 37 weeks. This study was approved by the French Commission Nationale de l'Informatique et des Libertés (CNIL).

Pregnancy dating was considered to be precise if it had been calculated from the date of the last period in a patient with regular menses (and provided there was less than 5 days deviation from term as predicted ultrasonographically), from an ultrasound scan before 20 weeks' gestation, and from the date of fertilisation in a woman who had undergone medically assisted reproduction. The preterm period studied was that between 24 and 37 weeks. Data collected enabled us to determine whether the preterm birth was spontaneous or iatrogenic.

2.2. Candidate predictors

The candidate predictors are: maternal age, body mass index (BMI) at the beginning of the pregnancy, smoking status during pregnancy, PAPP-A and free β-hCG, and obstetric history.

Assays of maternal serum PAPP-A and free β-hCG were performed between 11 weeks and 13 weeks + 6 days in a single laboratory kit and software (Perkin Elmer®), with adjustment for maternal weight, diabetes, racial origin and smoking status. PAPP-A and free β-hCG concentrations were expressed as multiple of the median (MoM). All other variables were expressed in binary form according to published data [4]: patients younger than 22 and older than 35 years old or between 22 and 35 years old, BMI below or above 19 kg/m^2, smoker or not. Previous deliveries were grouped as follows: fetal loss < 16 weeks, miscarriage between 16 and 24 weeks, preterm delivery between 24 and 27 weeks, 28 and 33 weeks, 34 and 36 weeks, and after 27 weeks. Comparisons between preterm delivery groups and deliveries after 37 weeks' gestation were then carried out using χ^2 tests. Mean PAPP-A and free β-hCG concentrations were compared using Student's *t*-test.

2.3. Model development

First of all, a predictive model was developed on the entire population. Then, three supplementary models were devised: a first model constructed on the group of patients who had had at least one prior pregnancy at or beyond 16 weeks, a second model which supplemented the initial model with a variable for occurrence of a threatened preterm delivery, and finally a third model which included occurrence or non-occurrence of a threatened preterm delivery in the subgroup of patients who already had at least one prior pregnancy that delivered at or beyond 16 weeks.

Threatened preterm delivery was defined as the presence of two or more uterine contractions every 10 min, with an ultrasonographic cervical length of ≤25 mm and/or clinical changes in the cervix, between 24 and 34 weeks' gestation.

Initially, a univariate analysis was performed in order to identify variables which might explain the occurrence of a preterm delivery by estimating the odds ratio (OR) and its 95% confidence interval (CI). Then ascending stepwise multivariate logistic regression models were built in the different data subset (variables were left in the model at a p-value < 0.05). ORs and their associated CI were computed for each predictor.

2.4. Model validation

The models obtained were validated by an external validation methodology with testing of the predictive models on a prospective sample of patients who had been selected using the same criteria as in the data acquisition sample, between 1 December 2011 and 30 June 2012.

2.5. Model performance

The performances of the different models were evaluated by receiver operating characteristic (ROC) curve analysis with estimation of areas under the curve (AUROC). The distribution of risks was used to calculate detection and false positive rates at different risk cut-offs. A p-value < 0.05 was considered as statistically significant. The statistical software package SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses.

3. Results

We included 33,761 patients with a singleton pregnancy receiving a consultation before 14 weeks' amenorrhoea, and which delivered after 24 weeks' gestation, between 1 January 2000 and 30 November 2011. We excluded 693 pregnancies in which gestational age had been imprecisely calculated, 146 cases of fetal death, 394 medical terminations of pregnancy on the grounds of fetal pathology and 694 iatrogenic preterm deliveries. In total, our series pooled 31,834 pregnancies in 26,320 patients, with 1188

Table 1
Maternal characteristics, obstetric history and biomarkers in the screened population.

Characteristics	Delivery ≥37weeks (n = 30,646)	Delivery <37 weeks (n = 1188)	p
Maternal age in years, mean	30.0	29.7	0.06
Maternal age ≤22 or ≥35, n (%)	8162 (26.6%)	351 (29.6%)	0.026
Body mass index (kg/m^2), mean	23.3	22.9	0.007
Body mass index ≤19 kg/m^2, n (%)	6586 (21.5%)	330 (27.8%)	<0.0001
Cicarette smoker, n (%)	3126 (18.7%)	138 (24.2%)	0.0008
Assisted medical procreation, n (%)	386 (1.2%)	25 (2.1%)	0.011
≥2 fetal losses <16 weeks, n (%)	449 (1.5%)	19 (1.6%)	0.71
Miscarriage at 16–23 weeks, n (%)	184 (0.6%)	17 (1.4%)	0.0004
Preterm delivery 24–27 weeks, n (%)	25 (0.1%)	4 (0.3%)	0.0042
Preterm delivery 28–33 weeks, n (%)	180 (0.6%)	21 (1.8%)	<0.0001
Preterm delivery 34–36 weeks, n (%)	760 (2.5%)	91 (7.7%)	<0.0001
Term delivery ≥37 weeks, n (%)	15,157 (49.5%)	412 (34.7%)	<0.0001
MoM PAPP-A, mean	0.96	0.84	0.0042
MoM free beta-HCG, mean	1.11	1.08	0.56

MoM, multiple of median.
PAPP-A and free beta-HCG assays were available for only 6514 patients.
Smoking status was known in only 17,341 cases.

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