Individualized assessment of preterm birth risk using two modified prediction models

Mariella Mailath-Pokorny [a], Stephan Polterauer [a,b,*], Maria Kohl [c], Verena Kueronyai [a], Katharina Worda [a], Georg Heinze [c], Martin Langer [a]

[a] Department of Obstetrics and Gynecology, Medical University Vienna, Vienna, Austria
[b] Karl Landsteiner Institute for General Gynecology and Experimental Gynecologic Oncology, Vienna, Austria
[c] Center for Medical Statistics, Informatics and Intelligent Systems, Medical University of Vienna, Vienna, Austria

A B S T R A C T

Objectives: To construct two prediction models for individualized assessment of preterm delivery risk within 48 h and before completed 32 weeks of gestation and to test the validity of modified and previously published models.
Study design: Data on 617 consecutive women with preterm labor transferred to a tertiary care center for threatened preterm delivery between 22 and 32 weeks of gestation were analysed. Variables predicting the risk of delivery within 48 h and before completed 32 weeks of gestation were assessed and applied to previously published prediction models. Multivariate analyses identified variables that were incorporated into two modified models that were subsequently validated.
Results: Two modified prediction models were developed and internally validated, incorporating four and six of the following variables to predict the risk of delivery within 48 h and before completed 32 weeks of gestation, respectively: presence of preterm premature rupture of membranes and/or vaginal bleeding, sonographic cervical length, week of gestation, fetal fibronectin, and serum C-reactive protein. The correspondence between the actual and the predicted preterm birth rates suggests excellent calibration of the models. Internal validation analyses for the modified 48 h and 32 week prediction models revealed considerably high concordance-indices of 0.8 (95%CI: [0.70–0.81]) and 0.85 (95%CI: [0.82–0.90]), respectively.
Conclusions: Two modified prediction models to assess the risk of preterm birth were constructed and validated. The models can be used for individualized prediction of preterm birth and allow more accurate risk assessment than based upon a single risk factor. An online-based risk-calculator was constructed and can be assessed through: http://cemsiis.meduniwien.ac.at/en/kb/science-research/software/clinical-software/prematurebirth/.

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Introduction

Preterm births account for 75% of perinatal mortality and more than half the long-term morbidity [1,2]. Preterm labor is now thought to be a syndrome initiated by multiple mechanisms, including infection or inflammation, utero-placental ischemia or hemorrhage, stress, and other immunologically-mediated processes [3]. The observation that several pathways are involved in its pathogenesis may explain why premature delivery has proved so difficult to predict and prevent [4,5]. A short cervical length and a raised cervicovaginal fetal fibronectin (fFN) concentration are the strongest predictors of preterm birth [6,7]. In addition several other accepted risk factors for preterm delivery include previous history of preterm birth, decidual hemorrhage manifested as vaginal bleeding, and infection [8–10]. Although preterm labor is one of the most common reasons for hospitalization of pregnant women, identifying women with preterm contractions who will actually deliver preterm is challenging and often imprecise [5]. Correspondingly, investigators have attempted to elucidate the factors that are associated

* Corresponding author at: Department of Obstetrics and Gynecology, Medical University, Waehringer Guertel 18 20, A 1090 Vienna, Austria.
Tel.: +43 1 40400 2962; fax: +43 1 40400 2911.
E-mail address: stephan.polterauer@meduniwien.ac.at (S. Polterauer).

with preterm delivery in order to prompt consideration of interventions when the risk of preterm delivery is high.

Nomograms depict predictive models which estimate the probability of a specific outcome [11]. They are widely applied tools in clinical practice and can be used to improve patient counseling and treatment planning [12]. However, only a few nomograms have been published in obstetrics [13–15]. Recently two models to predict preterm delivery within 48 h and before completed 32 weeks of gestation in women with preterm labor were constructed [13]. The aim of the present study was to construct two modified prediction models for assessment of preterm birth risk by incorporating relevant predictive parameters in order to allow individualized and accurate prediction of preterm birth.

Materials and methods

Patients

In this cohort study data were abstracted from a large single institution's database that was prospectively maintained and electronic medical records were reviewed. In this study all consecutive women between 22 and 32 weeks of gestation who were admitted for threatened labor to our tertiary perinatal center between 2007 and 2012 and delivered at the institution were eligible for inclusion. The diagnosis of threatened preterm delivery was based on clinical evidence of painful uterine contractions and/or cervical dilatation. Women were included, regardless of whether amniotic membranes were intact or ruptured. Gestational age was assigned on the basis of the last menstrual period and confirmed by first or early second-trimester sonography. Women whose pregnancies were complicated by preeclampsia, fetal growth restriction, in utero fetal death, or major fetal anomaly, and multiple gestation pregnancies were not included. The diagnosis of preterm labor was generally based upon clinical criteria of regular painful uterine contractions accompanied by cervical change shortening or contractions visible during contraction monitoring. Initial evaluation included cardiotocography, assessment of patient's past and present obstetrical and medical history, and assessment of gestational age. A speculum examination was performed and swabs for bacteriological cultures and for fetal fibronectin (fFN) were obtained. The presence of vaginal bleeding was documented. The diagnosis of preterm premature rupture of membranes (PPROM) was assessed clinically based on visualization of amniotic fluid in the vagina and confirmed by detection of placental alpha microglobulin-1. Trans-vaginal and trans-abdominal ultrasound examination to assess cervical length, maternal and fetal anatomic abnormalities, confirm the fetal presentation, assess amniotic fluid volume, and estimate fetal weight was performed. Serum blood samples were taken including blood count and assessment of serum C-reactive protein (CRP) levels (normal value <0.5 mg/dl). According to international guidelines two courses of betamethasone were administered to women with preterm uterine contractions who were considered high-risk (based on cervix length and fFN) for preterm birth before completed 32 weeks of gestation accompanied with administration of a tocolytic agent i.e. atosiban or hexoprenalin-sulfate. Appropriate antibiotics were administered to women with positive bacteriological culture results or clinical signs of infection and to women with PPROM. Time to delivery was calculated by the date and time of admission to the institution and the date and time of birth. Outcome variables were defined as delivery within 48 h and delivery before completion of 32 weeks of gestation.

Statistical analysis

Statistical methods are provided as annexed files.

Results

Patients

In total, 682 patients with premature labor who were admitted to the tertiary perinatal center at the Department of Obstetrics and Gynecology of the Medical University of Vienna between January 2007 and October 2012 and delivered at the institution were identified. Of these patients, 617 met the inclusion criteria, had all necessary variables documented, and were selected for analysis. Patient characteristics of the previously published Toulouse cohort and the Austrian cohort are provided in Table 1. Both cohorts were mainly composed of Caucasian women. One of the main differences between the two cohorts was a significantly higher rate of women who were admitted before 24 weeks of gestation in the Austrian cohort. Delivery rate within 48 h after transfer was slightly higher in the Austrian cohort, whereas delivery rates before completed 32 weeks of gestation were comparable between both cohorts. Mean (SD) CRP serum levels in the Austrian cohort was 1.3 (2.1) mg/dl, a positive fFN test was obtained in 128 (24.0%) of patients and the mean (SD) observed time between admission and delivery was 5.6 (5.4) weeks. Cumulative rates of women still pregnant after admission in relation to gestational week of delivery and time between

Table 1
Patient characteristics of the Austrian ($N=617$) and the published Toulouse ($N=737$) cohorts.

Parameter	Austrian cohort	Toulouse cohort
Maternal age at diagnosis (years)		
Mean	30	29
Gestational age at time of admission (weeks)		
Mean	27	29
N (%) < 24 weeks	145 (24)	17 (2)
N (%) 24–28 weeks	278 (45)	265 (36)
N (%) 29–32 weeks	194 (31)	455 (62)
History of preterm delivery or late miscarriage		
N (%)	95 (15.4)	103 (14.0)
Cerclage		
N (%)	37 (6.0)	21 (2.8)
Clinical characteristics at admission		
PPROM		
N (%)	159 (25.8)	172 (23.3)
Vaginal bleeding		
N (%)	37 (6.0%)	61 (8.3)
Functional cervical length (mm)		
Mean	18	17
N (%) < 15 mm	292 (48.0)	284 (38.5)
N (%) 15–25 mm	160 (26.3)	194 (26.3)
N (%) > 25 mm	156 (25.7)	259 (35.1)
Contractions requiring tocolysis		
N (%)	562 (91.1)	577 (78.3)
Outcome		
Delivery within 48 h	104 (16.9)	157 (21.3)
Delivery before 32 weeks of gestation	300 (48.6)	317 (43.0)

PPROM: preterm premature rupture of the membranes.