

Original Article

Early discrimination of preterm prelabour rupture of foetal membranes in nulliparous women

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ABSTRACT

INTRODUCTION. Preterm prelabour rupture of foetal membranes (PPROM), a subtype of spontaneous preterm birth (sPTB), affects 2-4% of all pregnancies and precedes 40-50% of preterm births. So far, only symptomatic treatment is available, underscoring the need for early identification to enable prophylactic intervention. The primary aim of this study was to explore the possibility of developing an early prediction model for PPRM, and secondarily sPTB, in nulliparous women.

METHODS. The risk of PPRM and sPTB (< 37 and < 34 gestational weeks) was assessed before 16 weeks of gestation using a discrete SuperLearner model applied to a large dataset (n = 36,269) obtained from the Copenhagen Pregnancy Cohort and national health registries. Predictor variables were selected based on research literature and hypothesised risks.

RESULTS. The prediction models proved clinically inadequate across all outcomes, reflected in low detection rates. For nulliparous women, discrimination of PPRM yielded a detection rate of 26.8% with a false positive rate (FPR) of 20%. For sPTB (< 37 and < 34 gestational weeks), the detection rates were 30.2% and 24.1%, respectively, using the same fixed FPR (20%).

CONCLUSIONS. The discrimination of PPRM and sPTB was clinically insufficient; however, these models could potentially be optimised by incorporating first-trimester biochemical and biophysical markers.

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TRIAL REGISTRATION. Not relevant.

Preterm birth, spontaneous or induced, refers to birth before 37 weeks of gestation (GW) [1]. It is either preceded by preterm contractions or by preterm prelabour rupture of foetal membranes (PPROM) before the onset of contractions [1]. PPRM affects 2-4% of all pregnancies, yields 40-50% of preterm births and carries the highest risk of neonatal mortality and morbidity among subgroups of spontaneous preterm birth (sPTB) [2].

PPROM remains an underreported research area [2], and alternatives to the currently predominant symptomatic identification and treatment are needed to allow for prophylactic treatment. Prediction models could support this effort, as these combine maternal characteristics, biochemical markers, and biophysical markers to assess the risk of adverse pregnancy outcomes [3]. However, prophylactic treatment for PPRM is limited. Prediction models could therefore provide insight into the pathoaetiology of PPRM to explore the potential use of existing

interventions, such as vaginal progesterone, or future interventions, potentially low-dose acetylsalicylic acid, assuming that several pregnancy conditions share a mutual pathology [4].

Notably, the well-established Copenhagen Pregnancy Cohort (CPC) provides extensive and unique patient-reported (PRO) data collected at the combined first-trimester prenatal screening programme at Copenhagen University Hospital – Rigshospitalet, attended by more than 90% of pregnant women in Denmark [5]. These data comprise maternal characteristics, socio-demographic factors, medical and obstetric history, mental well-being and lifestyle factors obtained through electronic questionnaires [5]. The information is subsequently transferred to the medical records, anonymised and made available for researchers following necessary approvals [5]. The CPC offers a valuable opportunity to assess risk factors for PPRM and sPTB, and to explore whether specific candidate predictors add any incremental predictive value.

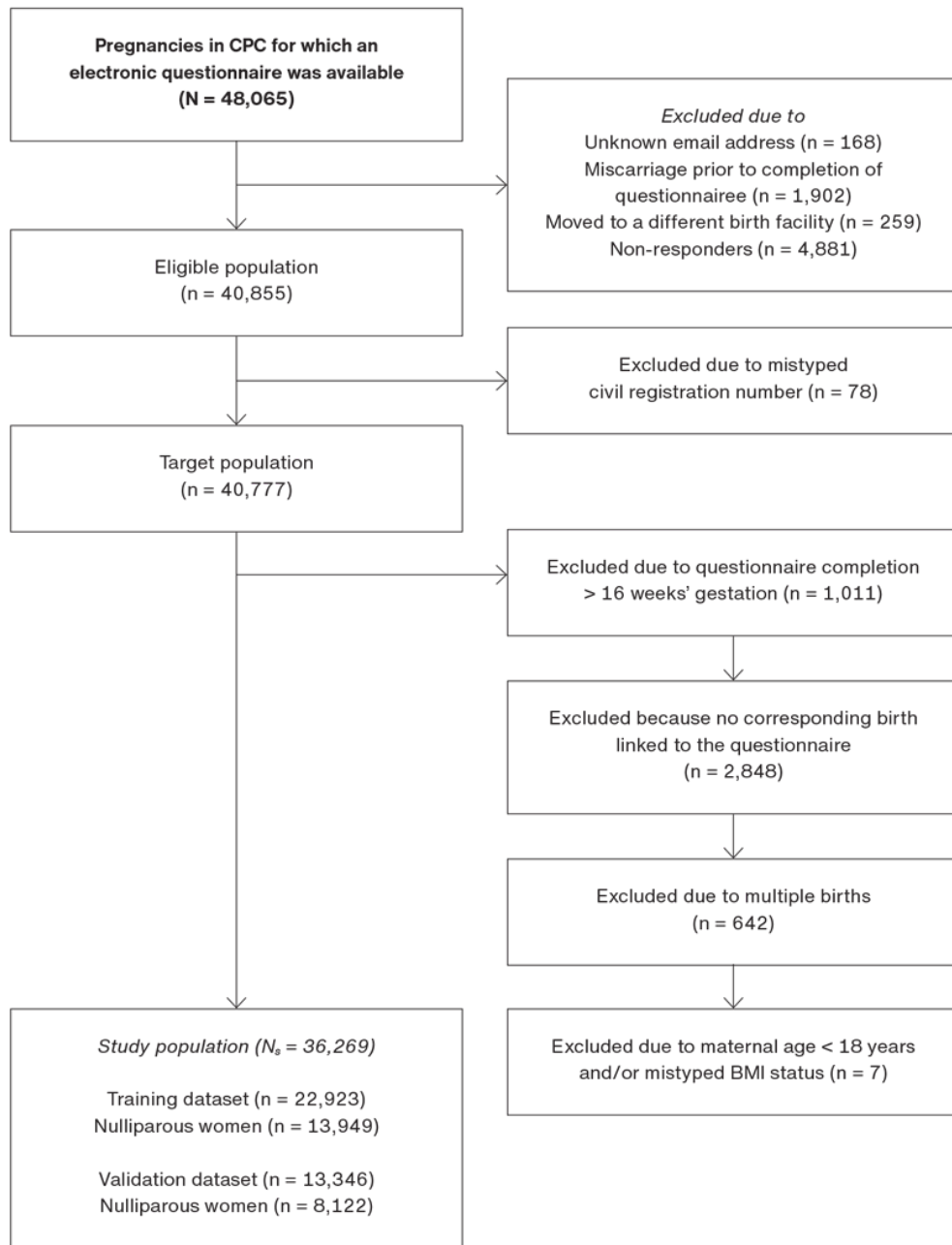
The overall aim of this study was to investigate whether early prediction (assessment < 16 GW) of primarily PPRM, and secondarily sPTB, based on comprehensive maternal and obstetric characteristics in nulliparous women, can provide insights into the underlying mechanisms of the conditions. The study focused on nulliparous women, as these women constitute a significant risk factor for PPRM [6].

Methods

Study population

Out of the 48,065 pregnancies in CPC (2012-2022), 40,855 questionnaires were initially eligible, after which the following exclusions were applied: Mistyped Danish civil registration number, completion of questionnaire > 16 GW, no corresponding birth with questionnaire, multiple births, < 18 years of age, and mistyped BMI (Figure 1). Data on the remaining pregnancies (n = 36,269) were linked with Danish health registries.

FIGURE 1 Flow chart of inclusion and selection of pregnancies in study population.



CPC = Copenhagen Pregnancy Cohort.

Statistical analysis

Discrimination of PPROM and sPTB was assessed using a random split dataset, thereby avoiding overfitting of one dataset [7]. This generated a training dataset (n = 22,923) (63.2%) and a validation dataset (n = 13,346) (36.8%). The socio-demographic characteristics of the study population were presented by medians with IQR, n, and %. Covariates were categorized into assumed risk factors and potential risk factors. The characteristics were described relative to PPROM (yes/no) and sPTB status (yes/no) for contextual comparison (Table 1). All analyses of multiparous women are provided in the supplementary file (Table S2, Table S6, Table S7). To perform the prediction, we applied a discrete SuperLearner model, which used ten-fold cross-validation to select the best-

performing model from a set of candidate models (**Table 2**) using the lowest Brier score [7]. We applied restricted cubic splines for non-linear relationships, including the continuous variables maternal age and pre-pregnancy BMI. For the covariate physical activity, we assumed that no answer implied an inactive state, showing no substantial change when missing values were removed in a sensitivity analysis. For history of previous conisation, previous sPTB and previous bleeding in early pregnancy, we assumed that the absence of a diagnosis code indicated that the event had not occurred or was not reported. Due to overlapping treatments, we performed a categorical ranking for assisted reproductive technology: 1) egg donation, 2) in vitro fertilisation/intracytoplasmic sperm injection and 3) hormone stimulation. The performance of each SuperLearner model was calculated based on the validation dataset and presented by a receiver-operating characteristic (ROC) curve with area under the characteristic curve (AUC) and corresponding 95% CI. Detection rates (DR) were determined based on a fixed false positive rate (FPR) of 20%. All analyses were conducted using R statistical software (RStudio, version 4.4.3).

TABLE 1 Socio-demographic characteristics of the women in the study population: nulliparous women ($N_{\text{tot}} = 22,070$).

Maternal characteristic	PPROM		sPTB	
	no ($N_{\text{no}} = 20,851$)	yes ($N_{\text{yes}} = 1,219$)	no ($N_{\text{no}} = 21,008$)	yes ($N_{\text{yes}} = 1,062$)
<i>Assumed risk factors</i>				
Maternal age:				
Median (IQR), yrs	30.3 (28.0-33.1)	30.8 (28.6-34.1)	30.3 (28.1-33.1)	31 (28.5-34.4)
Missing, n	-	< 5	-	< 5
Pre-pregnancy BMI:				
Median (IQR), kg/m ²	21.8 (20.2-23.9)	22.3 (20.5-24.4)	21.8 (20.2-24)	22 (20.4-24.3)
Groups, n (%):				
< 18.5 kg/m ²	1,025 (5.1)	50 (4.2)	1,014 (5.0)	61 (6.0)
18.5-24.9 kg/m ²	15,578 (77.6)	892 (75.1)	15,704 (77.6)	766 (75.0)
25-29.9 kg/m ²	2,638 (13.1)	178 (15.0)	2,676 (13.2)	140 (13.7)
≥ 30 kg/m ²	826 (4.1)	67 (5.6)	838 (4.1)	55 (5.4)
Missing, n	784	32	776	40
Education level, n (%):				
Higher degree: ≥ 5 yrs	11,236 (55.6)	672 (56.3)	11,377 (55.8)	531 (51.6)
Intermediate degree: 3-4 yrs	5,949 (29.4)	348 (29.1)	5,970 (29.3)	327 (31.8)
Short degree: 1-2 yrs	1,107 (5.5)	61 (5.1)	1,104 (5.4)	64 (6.2)
Technical degree	603 (3.0)	34 (2.8)	589 (2.9)	48 (4.7)
Compulsory education	1,319 (6.5)	79 (6.6)	1,339 (6.3)	59 (5.7)
Missing	637	25	629	33
Assisted reproductive technology, n (%):				
None	18,517 (88.8)	1,040 (85.3)	18,701 (89)	856 (80.6)
Egg donation	43 (0.2)	6 (0.5)	41 (0.2)	8 (0.8)
IVF/ICSI	504 (2.4)	22 (1.8)	476 (2.3)	50 (4.7)
Hormone stimulation	1,787 (8.6)	151 (12.4)	1,790 (8.5)	148 (13.9)
Missing	-	-	-	-
Smoking during the 1st trimester, n (%):				
Yes	241 (1.2)	22 (1.8)	242 (1.2)	21 (2.0)
Missing	348	6	334	20
Physical activity in the 1st trimester, n (%):				
Yes	13,279 (63.7)	766 (62.8)	13,409 (63.8)	636 (59.9)
Missing	-	-	-	-
Continent of origin, n (%):				
Africa	166 (0.8)	9 (0.7)	-	< 5
South and East Asia	835 (4.0)	66 (5.4)	864 (4.1)	37 (3.5)
North America	-	< 5	-	< 5
South America	145 (0.7)	8 (0.7)	146 (0.7)	7 (0.7)
Oceania	49 (0.2)	5 (0.4)	-	< 5
Europe	19,598 (94.0)	1,128 (92.5)	19,718 (93.9)	1,008 (94.9)
Missing	-	-	-	-
Cohabitation, n (%):				
Yes	18,936 (91.3)	1,093 (90)	19,084 (91.3)	945 (89.4)
Missing	-	< 5	100	5
Chronic medical disease, n (%):				
None	15,648 (75)	889 (72.9)	15,804 (75.2)	733 (69.0)
Somatic	4,530 (21.7)	268 (22.0)	4,511 (21.5)	287 (27)
Psychiatric	476 (2.3)	38 (3.1)	494 (2.4)	20 (1.9)
Somatic and psychiatric	197 (0.9)	24 (2.0)	199 (0.9)	22 (2.1)
Missing	-	-	-	-
<i>Potential risk factors</i>				
WHO-5 Well-Being Index:				
Median (IQR), points	64 (52-72)	64 (52-72)	64 (52-72)	64 (52-72)
Missing, n	-	< 5	127	10
Previous cervical conisation n (%):				
Yes	420 (2.0)	53 (4.3)	427 (2.0)	46 (4.3)
Missing	-	-	-	-
Previous abortion, n (%):				
Yes	5,662 (27.2)	346 (28.4)	5,726 (27.3)	282 (26.6)
Missing	-	-	-	-

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; PPRM = preterm prelabour rupture of foetal membranes; sPTB = spontaneous preterm birth.
a) To protect patient privacy, numbers below 5 are reported as < 5, and additional numbers are suppressed (-) to prevent back-calculation.

TABLE 2 Description of candidate models included in the SuperLearner model.

Model	Description
Model 0	Only previous sPTB or previous PPROM: only included for multiparous women ^a
Model 1	Additive effects of risk factors
Model 2	Like model 1 but contains a restricted cubic spline on maternal age: continuous
Model 3	Like model 1 but contains a restricted cubic spline on pre-pregnancy BMI: continuous
Model 4	Like model 1 but contains a restricted cubic spline on maternal age: continuous, and pre-pregnancy BMI: continuous
Model 5	Additive effect of risk factors and potential risk factors
Model 6	Like model 5 but contains a restricted cubic spline on maternal age: continuous
Model 7	Like model 5 but contains a restricted cubic spline on pre-pregnancy BMI: continuous
Model 8	Like model 5 but contains a restricted cubic spline on maternal age: continuous, and pre-pregnancy BMI: continuous
Model 9	Like model 1 but with pre-pregnancy BMI: categorical
Model 10	Like model 9 but contains a restricted cubic spline on maternal age: continuous
Null model	-

PPROM = preterm prelabour rupture of foetal membranes; sPTB = spontaneous preterm birth.

a) See supplementary file.

Main study outcomes

The main study outcome was PPROM, defined following the national guideline by the Danish Society of Obstetrics and Gynaecology, encompassing rupture of the foetal membranes < 37 GW before onset of contractions (usually > 1 hour) ([Table S1](#)) [8]. The secondary outcomes were sPTB < 37 GW and < 34 GW, referring to spontaneous preterm birth preceded by either PPROM or preterm contractions [1].

Predictor variables

The selection of predictors in the SuperLearner model was based on research literature [9-11] and assumed hypothesised risks. Specifications of origin of predictor variables, including diagnosis codes (International Statistical Classification of Diseases and Related Health Problems, tenth revision; ICD-10 codes), registry-/CPC derived, etc., are provided in [Table S3](#).

Approvals

Permission for data acquisition was granted by the Capital Region's Legal Department of Scientific Research (P-2022-676), Team for Medical Record Research (R-23054231 and R-21043472). The data were accessed through the Danish Health Authority (FSEID-00007045).

Trial registration: not relevant.

Results

Out of the 36,269 women included in the study, we focused on the 22,071 nulliparous women (60.9%). The data showed a high-resource study population with a normal median BMI (21.8-22.3 kg/m²), and the majority had a higher academic degree (≥ 5 years) ([Table 1](#)). The data demonstrated differences in maternal characteristics for

women with and without PPRM and sPTB (Table 1). The incidences of the following outcomes for nulliparous women were: PPRM 5.5% (n = 1,218), sPTB < 37 GW 4.8% (n = 1,062) and sPTB < 34 GW 1.5% (n = 343) (Table S4).

Building on pre-specified predictor variables, we defined ten candidate models for each outcome in the discrete SuperLearner model (Table 2) and selected them based on the lowest Brier score, showing differences in the best-performing models between PPRM and sPTB (Table S5).

The discrimination of PPRM for nulliparous women demonstrated an AUC of 0.566 (95% CI: 0.539-0.593) (Table 3). Prediction of sPTB < 37 and < 34 GW for nulliparous women yielded an AUC of 0.564 (95% CI: 0.533-0.596) and an AUC of 0.553 (95% CI: 0.499-0.607), respectively (Table 3).

TABLE 3 Receiver-operating characteristic curve with area under the characteristic curve calculated for each outcome for nulliparous women.

Outcome	AUC (95% CI)
PPROM	0.566 (0.503-0.659)
sPTB < 37 GW	0.564 (0.543-0.608)
sPTB < 34 GW	0.553 (0.535-0.645)

AUC = area under the characteristic curve; GW = gestational weeks; PPRM = preterm prelabour rupture of foetal membranes; sPTB = spontaneous preterm birth.

More specifically, prediction of PPRM for nulliparous women yielded a DR of 26.8% with a set FPR of 20% (Figure S1). The secondary outcomes sPTB < 37 and < 34 GW yielded DRs of 30.2% and 24.1%, respectively, with corresponding FPRs of 20% (Figure S1). The predictive performance for all outcomes was clinically insufficient, but discrimination of sPTB < 37 GW produced the most well-performing model. In comparison, the discrimination capability improved for multiparous women, but performance remained insufficient for clinical use (Figure S2) (Table S7).

Discussion

The study investigated the potential of early prediction of PPRM and sPTB (< 37 and < 34 GW) in nulliparous women based on maternal characteristics from PRO-data and health registries to gain information on risk factors and pathoetiology. The prediction models were developed in a high-resource population using a discrete SuperLearner model and pre-selection of predictor variables. The data showed that the predictive performance for all outcomes was clinically insufficient, e.g., a DR of 26.8% (FPR 20%) for discrimination of PPRM for nulliparous women.

Due to the low predictive performance in the current study, indicating that other predictors are needed, it would be highly relevant to explore whether biochemical markers could enhance model discrimination and provide new information. To date, a subset of studies have evaluated maternal first-trimester biomarkers for the discrimination of PPRM. Dhaifalah et al. displayed a DR of 82% (FPR 40%) when using azurocidin

concentrations at a cut-off of 1.29 ng/ml, whereas Ekin et al. reported a DR of 58% (FPR 38%) using mean platelet volume with a cut-off of ≤ 8.6 fl [12, 13]. Notably, in a recent systematic review, we outlined four first-trimester biomarkers: CRP, white blood cells (WBC), placental growth factor (PlGF), and soluble Fms-like tyrosine kinase-1 (sFlt-1), relevant for further investigation of an association with PPRM [14]. Additionally, Pregnancy Associated Plasma Protein-A (PAPP-A) has also shown promise [15]. Adding first-trimester concentrations of the mentioned biomarkers to our prediction model, either several in combination or as a stand-alone, could potentially improve predictive performance but would first and foremost provide further insight into the pathoetiology underlying these conditions. While cervical length screening alone may not be cost-beneficial for screening of preterm birth at a population level [16], a short cervix ≤ 25 mm at 11-14 weeks has been strongly associated with PPRM and serves as one of the most important maternal risk factors [6]. This supports the argument for integrating biochemical and biophysical markers, as these are known to improve first-trimester screening for chromosomal abnormalities and preeclampsia screening [3, 17].

A stronger – but still clinically insufficient discriminative ability – was demonstrated for multiparous women. In this group, the predictor variables previous PPRM, previous sPTB and previous bleeding in early pregnancy improved the predictive performance. Our findings are supported by research in the field, which shows that previous preterm birth is one of the most effective predictors of preterm birth, with a recurrence risk up to 35% [11].

A strength of our study is the inclusion of a large cohort ($n = 36,269$ women) with elaborate and unique information on maternal characteristics obtained through PRO data combined with data from national health registries, allowing us to test multiple predictor variables. In a future optimised prediction model, several of the selected predictor variables could be included, as these are routinely collected when booking first-trimester screening for chromosomal anomalies.

A limitation of our study is that we did not exclude chromosomal anomalies known to increase the risk of preterm birth [18]. Importantly, several predictor variables were not ideal for integration into the SuperLearner model. For example, for ethnicity, a known risk factor for all the included outcomes [1, 9], we specified ethnicity based on continent of origin for immigrants and their descendants, thereby categorising broadly. Research indicates that women of Black ethnicity have higher rates of preterm birth than women of Caucasian ethnicity, a disparity that may reflect both biological susceptibility and unequal access to quality of care across the world [1]. Detailed information on ethnicity was unavailable for this study. However, importantly, we know from the combined first-trimester prenatal screening that approximately 94% of the Danish population is Caucasian [17]. In the future, integrating ethnicity status retrieved from the Danish Fetal Medicine Database would be ideal [19].

Another challenge was using infection as a predictor variable, especially relevant for PPRM, as the condition is predominantly believed to result from an overactivation of inflammatory pathways [2]. The data set did not specify the timeframe of infection, making it impossible to assess whether it occurred in the first trimester. Including this variable would have required extensive investigation of the individual woman's medical journal, which was outside the study's scope and permissions. Another disadvantage was that several interesting variables showed skewed distributions, and some categories had a very low sample size, making them unsuitable for prediction. This resulted in the exclusion of alcohol intake or substance abuse as predictor variables, despite alcohol intake (> 4 drinks weekly) and use of narcotics (e.g., cocaine and opiates) having been associated with preterm birth [20]. However, we executed the SuperLearner model in a high-resource cohort, and their absence likely reflects the low prevalence of these exposures in the study population. Moreover, because the current dataset lacks information on a previous history of abdominal, vaginal cerclage and cervical insufficiency, we could not include these variables. Furthermore, changes in the registration of diagnosis codes might have occurred during the study period (e.g., conisation), reducing the credibility of this as a predictor variable. To

assess the potential significance of these variables, obstetric history on these matters should be collected differently in the future, potentially as part of national PRO data.

Conclusions

Despite comprehensive information, discrimination for both PPRM and sPTB was clinically insufficient, providing limited novel insights into the conditions and highlighting the need to include other novel predictors and different combinations of these predictors. Importantly, adding relevant first-trimester biochemical markers, either as stand-alone or in combination, to e.g. cervical length could potentially improve these models and provide sustainable information on pathoaetiology.

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References can be found with the article at ugeskriftet.dk/dmj

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Supplementary materials [a02260079-supplementary.pdf](#)

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