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Full length article

First-trimester prediction of preterm prelabour rupture of membranes incorporating cervical length measurement

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ABSTRACT

Objectives: To examine early pregnancy risk factors for preterm prelabour rupture of membranes (PPROM) and develop a predictive model.

Study design: Retrospective analysis of a cohort of mixed-risk singleton pregnancies screened in the first and second trimesters in three Danish tertiary fetal medicine centres, including a cervical length measurement at 11–14 weeks, at 19–21 weeks and at 23–24 weeks of gestation. Univariable and multivariable logistic regression analyses were employed to identify predictive maternal characteristics, biochemical and sonographic factors. Receiver operating characteristic (ROC) curve analysis was used to determine predictors for the most accurate model.

Results: Of 3477 screened women, 77 (2.2%) had PPROM. Maternal factors predictive of PPROM in univariable analysis were nulliparity (OR 2.0 (95% CI 1.2–3.3)), PAPP-A $<$ 0.5 MoM (OR 2.6 (1.1–6.2)), previous preterm birth (OR 4.2 (1.9–8.9)), previous cervical conization (OR 3.6 (2.0–6.4)) and cervical length $\leq$ 25 mm on transvaginal imaging (first-trimester OR 15.9 (4.3–59.3)). These factors all remained statistically significant in a multivariable adjusted model with an AUC of 0.72 in the most discriminatory first-trimester model. The detection rate using this model would be approximately 30% at a false-positive rate of 10%. Potential predictors such as bleeding in early pregnancy and pre-existing diabetes mellitus affected very few cases and could not be formally assessed.

Conclusions: Several maternal characteristics, placental biochemical and sonographic features are predictive of PPROM with moderate discrimination. Larger numbers are required to validate this algorithm and additional biomarkers, not currently used for first-trimester screening, may improve model performance.

Introduction

Preterm birth (PTB) is a major obstetric complication which occurs in more than 6% of pregnancies worldwide. [1] PTB is associated with high perinatal mortality and morbidity, and the risk of complications for the child, such as cerebral palsy, vision and hearing impairment, and learning disabilities, is inversely related to the gestational age at delivery. [2].

Spontaneous birth, initiated by preterm labour or preterm prelabour rupture of membranes (PPROM), accounts for about two thirds of all

Abbreviations: CL, cervical length; MoM, multiple of the median; PPROM, preterm prelabour rupture of membranes; PTB, preterm birth.

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deliveries before 37 weeks of gestation [1], and PPROM complicates approximately 1–3% of all pregnancies. [3–4] As for PTB, the pathophysiology of PPROM is diverse, [1] and complications are similar to those of spontaneous preterm labour, e.g. increased risk of Caesarean section, low birth weight, and hospitalisation of both mother and child. [5] Several risk factors for PPROM have been identified, some of which are potentially modifiable (i.e. smoking, body mass index <18.5 kg/m^2, diabetes mellitus and poor nutrition) and some are related to maternal obstetric history (i.e. previous PTB, prior cervical conization or a second trimester short cervical length (CL) and second trimester vaginal bleeding). [3,6–8].

No preventive treatment for PPROM has been documented, although a recent study suggests that low-dose aspirin prophylaxis might reduce the prevalence of PPROM in women screened at high risk for pre-eclampsia. [9] Improved early prediction of women at high risk for PPROM is important for further investigation of potential preventive interventions. Recently, El-Achi *et al.* [10] suggested that a predictive first-trimester model can be generated with information currently collected at 11–14 weeks of gestation, although with a modest screening performance.

The aim of this study was to examine early pregnancy risk factors for PPROM including first-trimester CL and further develop a predictive model for first-trimester screening for PPROM in a mixed-risk population.

Material and methods

This was a prospective study of a longitudinal cohort of pregnant women, who had undergone routine first- and second-trimester screening in Denmark. The cohort included asymptomatic women with a live singleton pregnancy attending for combined first-trimester screening between 1 November 2013 and 1 December 2014 at three large centers of fetal medicine in Denmark (Copenhagen University Hospital, Rigshospitalet; Aarhus University Hospital, Skejby; and Aalborg University Hospital). [11] Exclusion criteria were age <18 years, those unable to speak or understand Danish, congenital uterine anomaly, and a history-indicated cerclage or progesterone treatment at inclusion.

Participants were assigned to a transvaginal sonographic CL measurement at three time points: 1) combined first-trimester screening at 11–14 weeks, 2) fetal anomaly scan at 19–21 weeks and 3) an additional visit at 23–24 weeks of gestation. As described previously [11], all CL measurements were performed by trained staff according to Fetal Medicine Foundation guidelines using a Voluson E8 ultrasound machine (GE Medical Systems, Zipf, Austria) with a 5–9 MHz probe.

Information on maternal age, height, weight, ethnicity, mode of conception, smoking, pre-pregnancy diabetes mellitus, obstetric history (parity, first trimester vaginal bleeding, previous PTB <37 weeks) and prior conization, was recorded in the local Astraia databases (Astraia Software GmbH, Munich, Germany) at inclusion. Data on first-trimester biomarkers (free β-human chorionic gonadotropin (free βhCG) and pregnancy-associated plasma protein-A (PAPP-A) multiple of the medians (MoMs)) were also registered in Astraia. Assessment of gestational age was based on crown–rump length at combined first-trimester screening.

Data on pregnancy outcome were retrieved from local birth databases or patient files. The records of women delivering before 37 weeks of gestation were examined in detail to assess whether PTB was spontaneous, defined as spontaneous onset of labour or preterm rupture of membranes. PPROM was defined according to the national Danish guideline as rupture of membranes before 37 weeks of gestation with a latency of at least 1 h before onset of labour.

A standardized management protocol was followed recommending consultation with a maternal-fetal medicine specialist in case of a first-trimester CL ≤25 mm and that the CL measurement be repeated after 1–2 weeks. Likewise, women with second-trimester CL ≤25 mm were referred to a maternal-fetal medicine specialist and treated with vaginal progesterone (100–200 mg/day) and/or cervical pessary, at the discretion of the specialist in charge. Some cases of very short CL (≤15 mm) at 19–21 weeks (n = 5) or at 23–24 weeks (n = 1) were managed with cerclage. [11].

The study was approved by the Ethics Committee (H-1–2013-017) and the Danish Data Protection Agency (30–0945 and P-2021–814).

Statistical analysis

Data were analysed using Stata version 15.0 (StataCorp LLC, Texas, USA). Continuous variables were grouped into clinically relevant categories for maternal age, body mass index, maternal height, PAPP-A MoM and free βHCG MoM, and CL. Missing values were excluded from analysis. Trend test for an association with PPROM was performed in univariable logistic regression analyses. For dichotomous variables the χ^2 test was used. For all variables odds ratios (ORs) for logistic regression analyses were given with 95% confidence interval (CI).

Variables to be included in multivariable models were selected if the *P* value was < 0.10 in the univariable logistic regression analyses. The stepwise backward method was used, with exclusion of variables with the highest *P* value one at a time until the *P* value for at least one of the categories in the remaining variables was < 0.05. If a variable changed the point estimates for the adjusted ORs for PPROM by more than 10%, it was included in the final model (also if $P > 0.05$).

Variables in the final model were used to assess algorithms based on the β-coefficients. The discriminatory ability of the model was reported by the area (AUC) under the receiver operator characteristic (ROC) curve.

Results

There were 3477 women in the cohort with a mean maternal age of 30.6 years (standard deviation (SD) 4.5 years) and mean body mass index of 23.3 kg/m^2 (SD 4.2 kg/m^2). The vast majority were Caucasian (97.5%), non-smokers (97.3%) who had conceived spontaneously (90%) (Table 1). A total of 56% were nulliparous. First trimester bleeding, conization and previous PTB <37 weeks were registered in 6.7%, 6.6% and 2.9% of the women, respectively. The prevalence of pre-pregnancy diabetes mellitus was low (0.6%). Median free βhCG MoM was 1.01 (interquartile range (IQR) 0.7–1.4) and median PAPP-A MoM was 1.04 (0.7–1.5)).

The association between maternal characteristics and PPROM in univariable logistic regression analyses is detailed in Table 1. PPROM occurred in 77 (2.2%) of the women and was more frequent in women who were nulliparous ($P = 0.007$), had lower PAPP-A MoM (P trend = 0.007), had prior conization ($P < 0.001$) or had a history of PTB <37 weeks ($P < 0.001$). The OR for PPROM was 2.0 (95% CI 1.2–3.3) for nulliparous compared to multiparous women and was 2.6 (1.1–6.2) and 2.4 (1.1–5.3) for women with PAPP-A <0.5 MoM and 0.5–0.69 MoM, respectively, compared to women with PAPP-A >1.5 MoM. Women with prior conization had an OR for PPROM of 3.6 (2.0–6.4), and women with a history of PTB <37 weeks had an OR of 4.2 (1.9–8.9). There were no PPROM cases among the 20 women with pre-existing diabetes in this cohort. Neither smoking nor first trimester vaginal bleeding was associated with PPROM in this cohort.

The prevalence of a first-trimester CL <25 mm was low (0.4%), but there was a significant association with PPROM (OR 15.9 (95% CI 4.3–59.3)) (Table 2). The prevalence of second-trimester CL <25 mm was higher at 20 weeks (0.8%) and at 23 weeks (1.8%) and there were similar positive associations with PPROM (OR 15.5 (5.6–43.2) at 20 weeks and 18.9 (8.9–39.9) at 23 weeks).

The AUC was 0.69 (95% CI 0.61–0.76) in the most discriminatory first-trimester model without the CL measurements. This model included parity, PAPP-A MoM, conization and history of PTB <37 weeks. When first-trimester CL ≤25 mm was included in the model, the AUC was 0.72

Table 1
Maternal characteristics of the 3477 women in the cohort and the association with preterm prelabour rupture of membranes (PPROM) in univariable logistic regression analyses.

	Demographic	N	PPROM, n (%)	OR (95% CI)	P Value
Maternal age (years)	<25	259	8 (3.1)	1.2 (0.6–2.7)	0.10*
	25 to 29.9	1247	32 (2.6)	1.0 (reference)	
	30 to 34.9	1312	26 (2.0)	0.8 (0.5–1.3)	
	≥35	659	11 (1.7)	0.6 (0.3–1.3)	
BMI (kg/m^2)	<18.5	151	4 (2.7)	1.2 (0.4–3.4)	0.85*
	18.5 to 24.9	2456	54 (2.2)	1.0 (reference)	
	25.0 to 29.9	593	13 (2.2)	1.0 (0.5–1.8)	
	≥30	264	6 (2.3)	1.0 (0.4–2.4)	
	Missing	*13*	–	–	
Height (cm)	<165	858	24 (2.8)	1.3 (0.7–2.3)	0.24*
	165 to 169	1035	23 (2.2)	1.0 (reference)	
	170 to 174	969	17 (1.8)	0.8 (0.4–1.5)	
	≥175	615	13 (2.1)	1.0 (0.5–1.9)	
	Missing	*9*	–	–	
Ethnicity	Caucasian	3390	74 (2.2)	(reference)	0.43
	Other	87	3 (3.5)	1.6 (0.5–5.2)	
Pre-existing DM	No diabetes	3453	77 (2.2)	1.0 (reference)	0.80
	Type 1 DM	15	0	NA	
	Type 2 DM	5	0	NA	
Smokes cigarettes	No	3383	75 (2.2)	1.0 (reference)	0.97
	Yes	93	2 (2.2)	1.0 (0.2–4.0)	
	Missing	*2*	–	–	
Conception	Spontaneous	3128	65 (2.1)	1.0 (reference)	
	ART	170	4 (2.4)	1.1 (0.4–3.2)	0.81
	Insemination	161	7 (4.4)	1.5 (1.0–2.2)	0.06
	Unknown/other	18	1 (5.6)	1.4 (0.7–2.8)	0.33
Parity	Parous	1530	22 (1.4)	1.0 (reference)	0.007
	Nulliparous	1947	55 (2.8)	2.0 (1.2–3.3)	
First trimester vaginal bleeding	No	3243	72 (2.2)	1.0 (reference)	0.93
	Yes	234	5 (2.1)	1.0 (0.4–2.4)	
Prior cervical conization	No	3247	62 (1.9)	1.0 (reference)	<0.001
	Yes	230	15 (6.5)	3.6 (2.0–6.4)	
Previous preterm birth <37 weeks	No	3377	69 (2.0)	1.0 (reference)	<0.001
	Yes	100	8 (8.0)	4.2 (1.9–8.9)	
βhCG (MoM)	<0.5	309	4 (1.3)	0.8 (0.6–2.4)	0.94*
	0.5–0.69	581	14 (2.4)	1.4 (0.7–3.1)	
	0.7–1.49	1785	46 (2.6)	1.5 (0.8–3.9)	
	≥1.5	771	13 (1.7)	1.0 (reference)	
	Missing	*31*	–	–	
PAPP-A (MoM)	<0.5	315	11 (3.5)	2.6 (1.1–6.2)	0.007*
	0.5–0.69	498	16 (3.2)	2.4 (1.1–5.3)	
	0.7–1.49	1851	39 (2.1)	1.6 (0.8–3.1)	
	≥1.5	813	11 (1.4)	1.0 (reference)	

OR; odds ratio, CI; confidence interval, NA; not applicable, BMI; body mass index, DM; diabetes mellitus; ART; assisted reproductive technology, βhCG; β-human chorionic gonadotropin, PAPP-A; pregnancy-associated plasma protein-A, MoM; multiple of the median.
* P for trend.

(0.65–0.79). For the latter model approximately 30% of pregnancies later affected by PPROM would be identified in the first trimester for a false-positive rate of 10%. When substituting the first-trimester CL measurement with a measurement at 20 weeks the AUC was 0.73 (0.65–0.81) and at 23 weeks was 0.79 (0.72–0.86). According to this model, the detection rate for PPROM would increase to about 40% at 20 weeks and to 50% at 23 weeks for a false-positive rate of 10%.

Discussion

In this cohort study of nearly 3500 women, we found that first-trimester models were predictive of PPROM with moderate

Table 2
Distribution of cervical length measurements in the 3477 women in the cohort and association with preterm prelabour rupture of membranes (PPROM) in univariable logistic regression analysis.

	N	PPROM, n (%)	OR (95% CI)	P for trend
Cervical length at 11–14 weeks, mm				
<25	14	3 (21.4)	15.9 (4.3–59.3)	<0.001
25.0 to 29.9	283	9 (3.2)	1.9 (0.9–4.0)	
30.0 to 34.9	964	27 (2.8)	1.7 (1.0–2.8)	
≥35	2191	37 (1.7)	1.0 (reference)	
Missing	25	1	–	
Cervical length at 19–21 weeks, mm				
<25	26	5 (19.2)	15.5 (5.6–43.2)	<0.001
25.0 to 29.9	120	10 (8.3)	5.9 (2.9–12.2)	
30.0 to 34.9	542	21 (3.9)	2.6 (1.5–4.5)	
≥35	2646	40 (1.5)	1.0 (reference)	
Missing	143	1	–	
Cervical length at 23–24 weeks, mm				
<25	59	11 (18.6)	18.9 (8.9–39.9)	<0.001
25.0 to 29.9	159	5 (3.1)	2.7 (1.0–7.0)	
30.0 to 34.9	581	28 (4.8)	4.2 (2.5–7.0)	
≥35	2500	30 (1.2)	1.0 (reference)	
Missing	252	3	–	

OR; odds ratio, CI; confidence interval.

discrimination. Independent risk factors were nulliparity, low PAPP-A MoM, conization, history of PTB <37 weeks and a short first-trimester CL measurement.

Recently, El-Achi *et al.* [10] described the first attempt to create a first-trimester prediction model for PPROM and found an AUC of 0.67. The model in the El-Achi study included parity, maternal age, and body mass index, and the main risk factor was pre-existing diabetes, where the OR for PPROM was 6.7 (2.3–19.4) for Type 1 diabetes and 5.3 (1.6–18.3) for Type 2 diabetes. Interestingly, very few of the same predictors were included in our model for PPROM. Nulliparous women were at increased risk of PPROM in both the Australian and Danish cohort. However, in the Danish cohort there were few women with pre-existing diabetes, and none of these women had PPROM. Correspondingly, we found an AUC of 0.54 when applying the El-Achi prediction model to our cohort. It is, however, important to note, that the definition of PPROM was slightly different in these two studies, as El-Achi *et al.* classified women who laboured and delivered within 24 h of rupture of membranes as having spontaneous preterm labour rather than PPROM. Also, the two study populations had a different ethnic composition.

In our cohort the most important risk factors were short CL, previous PTB, and prior conization. Cervical length, measured by transvaginal ultrasound examination, is considered the best factor to identify the risk for PTB in the second trimester. [12] There is, however, still controversy regarding the role of CL measurement in the first trimester in the prediction of PTB. [11,13–15] Furthermore, a history of previous PTB, which is known to be an independent predictor of PTB [16], has been found to increase PPROM prediction if combined with a CL measurement in the second trimester. [17] Cervical surgery has been shown to predispose women to PTB, and this risk may be proportional to the amount of tissue removed from the cervix during the procedure. [18–20] Correspondingly, in our cohort we have previously shown that the combination of a first-trimester CL measurement with a history of PTB and conization yields an AUC of 0.79 for prediction of PTB and a detection rate of 50% for a 10% false-positive rate. [11] Our model for PPROM also included first-trimester PAPP-A MoM, but prediction remained moderate.

The findings of this study could be clinically useful for identifying a group of women who may benefit from more intense monitoring and intervention. Although there is no current data supporting a clear advantage of prophylactic interventions [21], there is evidence to suggest that aspirin prophylaxis for preterm preeclampsia might also reduce the occurrence of PPROM, potentially due to an anti-inflammatory effect. [9] Also, progesterone has been suggested to offer protection against PPROM through anti-microbial and anti-inflammatory actions. [22] Whilst the risk of spontaneous PTB is lowered by prophylactic progesterone treatment, in particular in women with a short CL, [23] progestogen administration does not prolong pregnancy in singleton gestations with PPROM. [24] No trials have been published evaluating the preventive effect of natural vaginal progesterone in women with PPROM. [25] In a large retrospective cohort of more than 20,000 singleton pregnancies, a significant reduction in PTB was observed among women who were routinely screened and treated for asymptomatic vaginal infections between 10 and 16 weeks' gestation [26] and this may be a useful intervention in those screening at high risk for PPROM.

Additional biomarkers not currently used for first-trimester screening may improve PPROM prediction model performance. Several have been identified, although most have been examined in the second trimester or later, rather than in the first trimester. Women with PPROM have a significantly increased platelet count as well as lower mean platelet volume in the first trimester. [27] In a large retrospective cohort study, first trimester anemia was associated with an increased risk of subsequent PTB [28] and first trimester leukocytosis was associated with an increased risk of PTB, but with no significant difference for PPROM. [29] Whereas Banaem *et al.* [30] found that C-reactive protein concentration was higher in the first 20 weeks of pregnancy in women who later developed PPROM, Bakalis *et al.* [31] did not find an association with plasma C-reactive protein concentration at 11–13 weeks. A less readily available test associated with inflammation in human gestational tissue is advanced glycation end products (AGEs). [32] Serum maternal AGEs was found to be significantly increased at 11–13 weeks of gestation in women destined to develop PPROM or deliver preterm, [33] and this marker may be useful for first trimester prediction of PPROM. Thus, although infection and inflammation are both associated with PPROM, results for first trimester inflammatory markers are ambiguous. Recent studies have identified genetic markers including plasma cell-free RNA markers associated with risk of PTB [34–38], where some related to inflammation and immune response were specifically associated with an increased risk of PPROM when measured as early as 20 weeks' gestation. [37].

In the current study, a prospective study design with virtually complete outcome data, including a first-trimester CL measurement

recorded in 99% of the women, is a strength. Further, important potential risk factors for PPROM such as previous PTB, prior conization, and first trimester bleeding in pregnancy were registered. For all women with PTB <37 weeks of gestation, the patient file was scrutinized to assess onset of labour and rupture of membranes. However, the exact timing of the interval between rupture of membranes and labour onset was not registered, and it was therefore not possible to use a more restrictive definition of PPROM as in the El-Achi study. Using a time limit of 24 h might lead to identification of different risk factors for PPROM, as some women classified as PPROM in our cohort would instead be classified as spontaneous preterm labour. Despite our relatively large sample size there were insufficient numbers of key candidate predictors such as bleeding in early pregnancy and pre-existing diabetes to include in the models, and information on additional risk factors such as bacteriuria, Group B Streptococcus status as well as cone depth were not available in the dataset. Information about other risk factors such as additional chronic diseases, invasive prenatal diagnostic procedures, or short inter-pregnancy interval was not available for this study. Finally, use of aspirin was not registered in our cohort. Until 2017, the Danish national preeclampsia guideline recommended giving 75 mg aspirin daily from 12 to 37 weeks to women having at least one National Institute for Health and Care Excellence (NICE) high-risk factor for preeclampsia, and this has been shown to be the case for only about 3.5% of all Danish births. [39].

Conclusion

Several features including maternal characteristics, placental biomarkers and sonographic features are predictive of PPROM in the first trimester with moderate discrimination (AUC 0.7–0.8). Larger study populations are required to validate this algorithm, and additional biomarkers not currently used for first-trimester screening may improve model performance. Further utility studies of various interventions in high-risk women are needed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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