Fetal Diagnosis and Therapy

Original Paper

Fetal Diagn Ther 2020;47:624–629
DOI: 10.1159/000506541

Received: November 16, 2019
Accepted after revision: February 13, 2020
Published online: April 8, 2020

# First-Trimester Prediction of Preterm Prelabour Rupture of Membranes

Vanessa El-Achi[a] Bradley de Vries[a] Cecelia O'Brien[a, b] Felicity Park[c] Jane Tooher[a] Jon Hyett[a, c]

[a]Sydney Institute for Women, Children and their Families, Royal Prince Alfred Hospital, Sydney, NSW, Australia; [b]Department of Maternal and Fetal Medicine, Townsville Hospital, Townsville, QLD, Australia; [c]Discipline of Obstetrics, Gynaecology and Neonatology, Central Clinical School, Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

**Keywords**
Pregnancy · Preterm prelabour rupture of membranes · Risk factors · Prediction · First trimester

**Abstract**
***Background:*** Preterm prelabour rupture of membranes (PPRoM) is commonly associated with preterm delivery and affects up to 3% of all pregnancies. It is associated with high rates of morbidity and mortality for the mother and the newborn. ***Objectives:*** To identify risk factors for PPRoM and develop a model for first-trimester prediction of risk of PPRoM. ***Methods:*** A retrospective analysis of a series of women who had first-trimester (11–$13^{+6}$ weeks) screening for aneuploidy and pre-eclampsia and delivered in the same institution was performed. Univariate and multivariate logistic regression analyses were used to identify maternal and pregnancy factors and then develop a clinical prediction model for PPRoM. ***Results:*** 10,280 women were screened between April 2010 and October 2016. 144 (1.4%) had PPRoM. Maternal factors predictive of PPRoM included nulliparity (parous women, OR 0.53; 95% CI 0.4–0.8), pre-existing diabetes mellitus (DM) (Type 1 DM, OR 6.7; 95% CI 2.3–19.4, Type 2 DM, OR 5.3; 95% CI 1.6–18.3), maternal age group ($p = 0.004$), and BMI category ($p = 0.012$). Uterine artery pulsatility index (UAPI) and biochemical parameters (PAPP-A, free βHCG) did not reach statistical significance. The predictive model had moderate efficacy with an area under the ROC curve of 0.67. ***Conclusions:*** Several maternal characteristics collected during first-trimester screening predict PPRoM. Biomarkers currently measured during first-trimester screening (PAPP-A, βHCG, and UAPI) do not predict PPRoM. Whilst a predictive model can be generated with information currently collected at 11–$13^{+6}$ weeks, this has only modest screening performance. First-trimester screening provides a structured framework where other predictors could improve model performance, and future studies should focus on the addition of other risk factors and biomarkers that may improve screening efficacy.



## Introduction

Preterm prelabour rupture of membranes (PPRoM) is associated with one third of preterm births [1, 2] and complicates 1–3% of all pregnancies [3, 4]. Compared with other preterm infants, those born following PPRoM have higher rates of perinatal mortality due to infection,

karger@karger.com
www.karger.com/fdt



Dr. Vanessa El-Achi
RPA Women and Babies, Royal Prince Alfred Hospital
Missenden Road
Camperdown, NSW 2050 (Australia)
vanessa.elachi@health.nsw.gov.au

birth trauma, and respiratory disease [5, 6]. PPRoM is an independent risk factor for respiratory distress syndrome, sepsis, and cerebral palsy [7–9], and it is associated with specific complications of oligohydramnios such as skeletal deformities and pulmonary hypoplasia [10]. PPRoM is also associated with maternal morbidity due to prolonged antenatal hospital admission, caesarean section and post-traumatic stress syndrome [11].

The aetiology of PPRoM is thought to be multifactorial, including infection, inflammation, vascular disease and uterine over-distension, and the final common pathway is believed to involve the inflammatory cascade [4, 12]. Identified risk factors for PPRoM include a maternal history of preterm birth (secondary to either spontaneous preterm labour or PPRoM), previous cervical surgery, and cervical shortening on transvaginal ultrasound scan [13, 14]. Genital and urinary tract infections have also been implicated [2, 4, 15, 16]. Maternal conditions such as pre-pregnancy obesity, drug dependence, poor nutrition, mental health disorders, and pre-existing diabetes mellitus (DM), hypertension, and thyroid disease [14, 17–19] have recognised associations. Pregnancy-related risk factors include antepartum haemorrhage, placental abruption, and factors that distend the uterus such as polyhydramnios and multiple pregnancy [4, 14, 16–20]. Other authors have suggested that inflammatory biomarkers, such as C-reactive protein, may be associated with PPRoM [21]. The common associations with features of placental insufficiency and of underlying inflammation have led many authors to suggest that adverse outcomes such as pre-eclampsia, spontaneous preterm labour, and PPRoM lie on a spectrum rather than being isolated conditions [22].

To date, prediction of PPRoM has been problematic as most women who develop this complication have no identifiable risk factors [16]. Despite this, it is likely that early identification of those at risk of PPRoM, followed by implementation of prophylactic intervention, will be necessary for prevention. A number of different treatment strategies have been suggested – although it is important to acknowledge that at this point in time, data supporting a clear advantage of prophylactic interventions are not readily available [23, 24]. Given the final common inflammatory pathway, some authors have suggested that anti-inflammatory agents may have a role to play in the prevention of PPRoM [23]. It is again interesting to note that aspirin is of significant value in reducing rates of early onset of pre-eclampsia (ePET) and has also been shown to have an independent effect on the prevalence of preterm birth [25–27]. As there may be both aetiological and therapeutic links between PPRoM and other adverse outcomes, we hypothesise that it might be possible to use current first-trimester screening markers for conditions like pre-eclampsia as the basis of a screening test for PPRoM. If these markers could be used to screen for multiple adverse outcomes this would reduce the cost of predictive screening. The purpose of this study was to determine whether maternal characteristics and biomarkers currently used in first-trimester screening could also be used to screen for PPRoM and to develop an algorithm for risk prediction for PPRoM.

## Materials and Methods

This was a retrospective study of a longitudinal cohort of women who were screened in the first trimester of pregnancy at a tertiary hospital in Sydney, Australia.

*Population*

Data were collected for women presenting to the Royal Prince Alfred Hospital for combined first-trimester screening at $11–13^{+6}$ weeks' gestation from April 16, 2010, to October 7, 2016. Exclusion criteria included multiple pregnancy, loss to follow-up after first-trimester screening and termination of pregnancy.

The cohort from April 1, 2012, to October 7, 2016, was treated with 150 mg aspirin if they were defined as high risk for ePET, based on results of screening using the validated Fetal Medicine Foundation algorithm [27, 28]. The earlier cohort, from April 16, 2010, to March 9, 2012, were not treated with aspirin. Women screened between March 10 and 31 were deemed to have been seen in a transition period and were excluded from subsequent data collection and analysis. All women (regardless of ePET risk and aspirin treatment) were included, since we showed in a previous study that aspirin prescribed on the basis of the ePET risk did not significantly affect the risk of PPRoM [29].

PPRoM was defined as the rupture of membranes before the onset of contractions prior to 37 weeks' gestation [1]. PPRoM was differentiated from spontaneous preterm labour, defined as births at less than 37 weeks' gestation with the onset of contraction and cervical change with intact membranes [18]. We classified women who laboured and delivered within 24 h of rupture of membranes as having spontaneous preterm labour rather than PPRoM.

*Data*

Data for demographics, pregnancy, and neonatal outcomes were collated from the Fetal Medicine database (Viewpoint version 5.6.9.483; GE Healthcare, Frankfurt, Germany) and the hospital maternity information system (Powerchart; Cerner, Kansas City, MO, USA). The formal hard copy medical record was also reviewed if delivery occurred before 37 weeks' gestation or when the electronic record was incomplete.

Demographic and pregnancy-related data were collected including ethnicity, parity, pre-existing DM, maternal age, body mass index (BMI), height, cigarette smoking, pregnancy-associated plasma protein A (PAPP-A), beta human chorionic gonadotrophin (βHCG), and mean uterine artery Doppler pulsatility index (UAPI).

**Table 1.** Univariate logistic regression of the women included in the retrospective cohort

| Demographics | *n* | OR (95% CI) | *p* value |
|---|---|---|---|
| Ethnicity | | | 0.21 |
| Caucasian | 6,804 | 1.0* | |
| Asian | 2,608 | 0.8 (0.6–1.2) | |
| South Asian | 774 | 1.6 (0.9–2.6) | |
| African | 120 | 0.6 (0.1–4.2) | |
| Parity | | | 0.009 |
| Parous | 4,306 | 1.0* | |
| Nulliparous | 5,994 | 1.6 (1.1–2.3) | |
| Pre-existing DM | | | <0.001 |
| No diabetes | 10,230 | 1.0* | |
| Type 1 DM | 46 | 6.9 (2.4–19.5) | |
| Type 2 DM | 31 | 7.8 (2.3–25.9) | |
| Maternal age, years | | | 0.03 |
| <25 | 415 | 1.0* | |
| 25<30 | 2,069 | 0.5 (0.2–1.2) | |
| 30<35 | 4,396 | 0.6 (0.3–1.3) | |
| 35+ | 3,427 | 1.0 (0.5–2.0) | |
| BMI, kg/m$^2$ | | | 0.006 |
| <20 | 1,015 | 1.0* | |
| 20<25 | 5,579 | 0.9 (0.5–1.5) | |
| 25<30 | 2,539 | 1.0 (0.6–1.9) | |
| 30+ | 1,173 | 1.9 (1.0–3.6) | |
| Height, cm | | | 0.08 |
| <155 | 978 | 1.0* | |
| 155<160 | 1,908 | 1.0 (0.6–1.7) | |
| 160<165 | 2,771 | 0.6 (0.4–1.1) | |
| 165<170 | 2,574 | 0.7 (0.4–1.2) | |
| ≥170 | 2,073 | 0.5 (0.3–1.0) | |
| Smokes cigarettes | | | 0.09 |
| No | 10,041 | 1.0* | |
| Yes | 264 | 1.9 (0.9–4.2) | |
| PAPP-A, MoM | | | 0.08 |
| <0.5 | 834 | 1.0* | |
| 0.5<1 | 3,632 | 0.8 (0.5–1.4) | |
| 1<1.5 | 2,928 | 0.6 (0.3–1.1) | |
| 1.5<2 | 1,525 | 0.6 (0.3–1.2) | |
| ≥2 | 1,376 | 0.4 (0.2–0.8) | |
| βHCG, MoM | | | 0.80 |
| <0.5 | 989 | 1.0* | |
| 0.5<1 | 3,786 | 0.8 (0.5–1.4) | |
| 1<1.5 | 2,519 | 0.7 (0.4–1.3) | |
| 1.5<2 | 1,348 | 0.8 (0.4–1.5) | |
| ≥2 | 1,656 | 0.9 (0.5–1.7) | |
| Mean UAPI, MoM | | | 0.29 |
| <1 | 3,314 | 1.0* | |
| 1<1.1 | 3,495 | 1.4 (0.9–2.1) | |
| 1.1<1.2 | 2,184 | 1.5 (0.9–2.3) | |
| ≥1.2 | 1,274 | 1.1 (0.6–2.0) | |

* Reference group. DM, diabetes mellitus; BMI, body mass index; PAPP-A, pregnancy-associated plasma protein A; MoM, multiple of the median; βHCG, beta human chorionic gonadotrophin; UAPI, uterine artery Doppler pulsatility index.

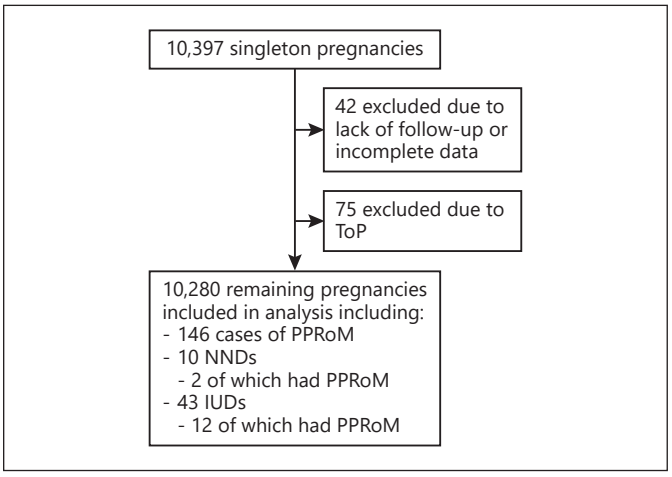


**Fig. 1.** A flow chart describing the number of women included in our retrospective cohort study. ToP, termination of pregnancy; NND, neonatal death; IUD, intrauterine death.

*Statistical Analyses*

Data were analysed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). A $p$ value of <0.05 was considered statistically significant. Statistical analysis included the Mann-Whitney U test for comparing distributions of non-parametric data, the $t$ test for comparing means of normally distributed continuous data, and the $\chi^2$ test for comparing categorical outcomes.

Continuous variables were tested for linear association with the logit function of the outcome (PPRoM) by grouping into 4–5 clinically relevant categories (such as BMI, maternal age, and maternal height) or grouped by MoM (multiple of the median) (for PAPP-A, βHCG, and UAPI) and plotting the β-coefficients against the mid-points of each group. Non-linearly associated variables were analysed by group. Explanatory variables were selected for multivariable models if $p < 0.25$ in the univariate logistic regression. The stepwise backward method was used, excluding variables with the highest $p$ value one at a time until the remaining variables were <0.05. If a variable changed the point estimates for the adjusted odds ratios (ORs) for PPRoM (even if $p > 0.05$) by more than 10%, it was retained in the model. Interaction was assessed by creating interaction terms among variables where interaction was considered clinically plausible, with a cut-off of 0.05 for inclusion of the term. Co-linearity was considered present when the variance inflation factor was >10. Variables in the final model were used to create an algorithm based on the β-coefficients in the linear predictor. Goodness of fit was assessed by the Hosmer-Lemeshow test, and the discriminatory ability of the model was measured by concordance (equivalent to the area under the ROC curve).

## Results

A total of 10,397 singleton pregnancies were screened between April, 16, 2010, and October, 7, 2016 (Fig. 1). 42 women were excluded due to lack of follow-up or incomplete data. 75 were excluded due to a severe structural or

**Table 2.** Multivariate logistic regression – variables from the univariate logistic regression (Table 1) that reached statistical significance or were close to significance were analysed in a multivariate logistic regression

| Variables | OR (95% CI) | *p* value |
|---|---|---|
| Parity | | 0.0006 |
| Nulliparous | 1.0* | |
| Parous | 0.53 (0.4–0.8) | |
| Pre-existing diabetes | | <0.0001 |
| No DM | 1.0* | |
| Type 1 | 6.7 (2.3–19.4) | |
| Type 2 | 5.3 (1.6–18.3) | |
| Maternal age, years | | 0.004 |
| <25 | 1.0* | |
| 25≤30 | 0.6 (0.3–1.3) | |
| 30≤35 | 0.7 (0.3–1.6) | |
| ≥35 | 1.3 (0.6–2.7) | |
| BMI, kg/m$^2$ | | 0.012 |
| <20 | 1.0* | |
| 20≤25 | 0.8 (0.4–1.4) | |
| 25≤30 | 0.9 (0.5–1.6) | |
| ≥30 | 1.6 (0.8–3.1) | |
| Height, cm | | 0.058 |
| <155 | 1.0* | |
| 155≤160 | 1.0 (0.6–1.8) | |
| 160≤165 | 0.6 (0.3–1.1) | |
| 165≤170 | 0.7 (0.4–1.2) | |
| ≥170 | 0.7 (0.3–1.0) | |
| PAPP-A, MoM | | 0.078 |
| <0.5 | 1.0* | |
| 0.5≤1 | 0.8 (0.5–1.4) | |
| 1≤1.5 | 0.6 (0.3–1.1) | |
| 1.5≤2 | 0.6 (0.3–1.2) | |
| ≥2 | 0.4 (0.2–0.8) | |

* Reference group.
For abbreviations, see text or Table 1.

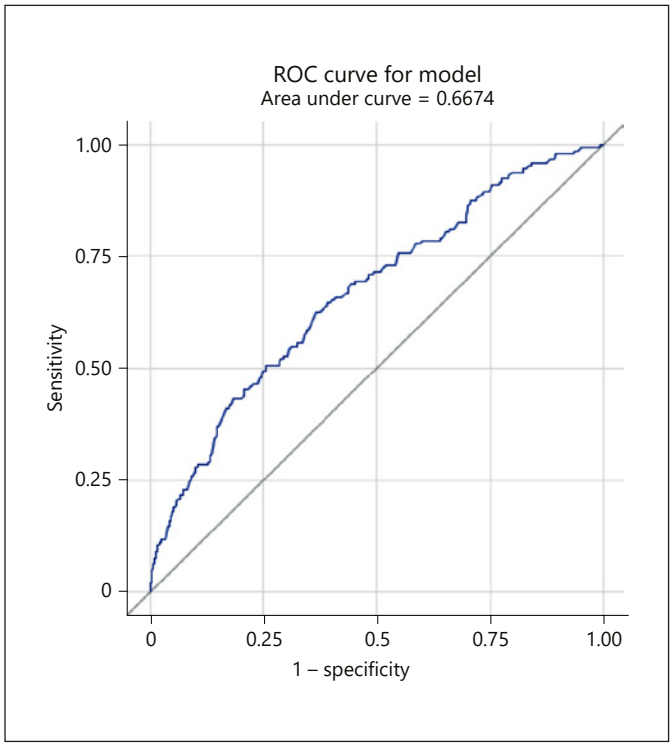


**Fig. 2.** Receiver Operator Curve (ROC) for the PPRoM model, showing an area under the curve of 0.67.

chromosomal abnormality and subsequent termination of pregnancy. The remaining 10,280 ongoing pregnancies included 43 intrauterine deaths, of which 12 had PPRoM <24 weeks. There were also 10 neonatal deaths within 1 week of delivery (2 of which had PPRoM). Overall, there were 144 cases of PPRoM (1.4%, 144/10 280) during this study period included in the analysis.

The mean maternal age was 32.7 years old (standard deviation [SD] 4.5), and mean BMI was 24.6 (SD 4.7). The mean foetal crown-rump length at time of screening was 65.5 mm (SD 7.6), with a mean nuchal translucency of 1.89 mm (SD 0.5). 58% of all women were nulliparous, and 97.4% were non-smokers.

In the univariate logistic regression analysis, nulliparity (OR 1.6; 95% CI 1.1–2.3, $p$ 0.009), pre-existing DM (Type 1 DM, OR 6.9; 95 % CI 2.4–19.5, $p < 0.001$, Type 2 DM, OR 7.8; 95% CI 2.3–25.9, $p < 0.001$), increasing maternal age ($p = 0.03$), and increasing BMI ($p = 0.006$) were statistically significant risk factors for PPRoM (Table 1). Ethnicity and smoking were not statistically significant risk factors. PAPP-A <0.5 MoM had a lower risk of PPRoM compared with PAPP-A >2.0 MoM (OR 0.4; 95% CI 0.2–0.8, overall $p$ value for PAPP-A = 0.08). There was a possible association between maternal height and PPRoM ($p = 0.08$). We did not find an association between serum βHCG ($p = 0.8$) or mean UAPI and PPRoM ($p = 0.29$).

Multivariable analysis identified parity, pre-existing DM, maternal age, and BMI as independent risk factors for PPRoM (Table 2). Pre-existing DM was the strongest risk factor for PPRoM in this study. The variables from the multivariable analysis were incorporated into a model for predicting PPRoM. The area under the ROC curve was 0.67 (Fig. 2). Approximately 25% of all pregnancies that will continue to be affected by PPRoM are identified for a screen positive rate of 10%.

## Discussion

This retrospective cohort study from a large tertiary hospital in Sydney, Australia, is the first to attempt to create a first-trimester prediction model for PPRoM. We identified specific risk factors for PPRoM including nulliparity, pre-existing DM, increased maternal age and high BMI, which could be incorporated into a clinical prediction model to estimate the risk of developing PPRoM.

Nulliparity was a statistically significant risk factor for PPRoM which is consistent with previous studies [30]. Pre-existing Type 1 or Type 2 DM was also shown to be an important risk factor for PPRoM, consistent with previous data [18]. Increased maternal age (≥35 years of age) has been previously shown to be a risk factor for PPRoM and was confirmed in our analysis [30]. In a previous study, increased BMI (≥30 kg/m$^2$) was shown to be associated with PPRoM but did not reach statistical significance [30]. Of the risk factors identified, only BMI is modifiable, highlighting the importance of maintaining a healthy weight before pregnancy.

In our study, ethnicity and smoking were not found to be statistically significant risk factors, but there are conflicting data regarding the effect of these variables [1, 14, 17, 30]. There was a tendency towards PPRoM with a PAPP-A <0.5 MoM, consistent with one other study [31]. We did not find an association between maternal serum concentrations of free βHCG or mean UAPI. A previous study identified high free βHCG as a risk factor for PPRoM [32], whereas UAPI has not been studied previously.

To our knowledge, this is the first study to design a prediction model for PPRoM. The area under the ROC curve was 0.67, indicating that our model is fair, but requires further research and improvement. A likely simple but effective way of improving this model could be to include additional known risk factors for PPRoM such as a history of PPRoM and preterm birth, genito-urinary infection, and a history of bleeding in pregnancy; unfortunately, this history was not comprehensively collected in our first-trimester screening cohort; however, it should be considered for any future studies of this kind. For example, in other datasets, a previous history of PPRoM has a 3.3-fold increase in preterm birth caused by PPRoM and a 14-fold higher risk of PPRoM before 28 weeks [33]. Ideally, future studies would be conducted prospectively and would include these variables.

There are further limitations to this study. Whilst our study cohort in Sydney was unselected, they do constitute a group of women who chose to have first-trimester screening for aneuploidy, and other women could have had different baseline risks. Also, the socio-economic and ethnic composition of this community may not reflect the general obstetric population. Furthermore, due to the retrospective nature of this study, many important risk factors for PPRoM were not included because such data were not collected in the database. The inclusion and analysis of such characteristics and variables as possible risk factors of PPRoM, analysed in a prospective study, may improve our prediction model, as the current model which was developed in this study does not perform well enough to be applied in a clinical or research setting. Details which should be collected prospectively for future studies should include known important risk factors for PPRoM such as a history of PPRoM or preterm birth, second-trimester miscarriage, previous cervical surgery, and a history of bleeding in pregnancy. In addition, the identification and inclusion of first-trimester biomarkers for PPRoM into any future algorithm could be important to increase its accuracy such that it could be used clinically. We are currently planning a pilot study to examine potential biomarkers which could be included. Once a suitable model for predicting PPRoM has been developed, possible interventions for women screened as high risk could be explored. We are currently researching potential preventative interventions that could be trialled once a validated model has been developed. Future studies should aim to refine the model for predicting PPRoM, ideally in a prospective trial. Subsequent models should be validated, then proceed to a large interventional trial, with the aim of reducing the prevalence of PPRoM through targeted and specialised antenatal care.

## Conclusion

PPRoM is a common complication of pregnancy associated with significant morbidity and mortality. This study has identified four key risk factors for PPRoM: nulliparity, DM, maternal age and BMI, that are typically collected as part of routine first-trimester screening. None of the investigational tools used during first-trimester screening were of benefit in a predictive model for PPRoM. Further refinement of this predictive model is required prior to implementation as a clinical tool.

## Statement of Ethics

Ethics approval was obtained from the Royal Prince Alfred Human Research Ethics Committee (RPAH HREC 11 0305).

## Disclosure Statement

The authors do not have any conflicts of interest to declare.


## Funding Sources

No specific funding was obtained for this study.


## Author Contributions

Jon Hyett was responsible for the concept, design, and planning this study. Jane Tooher helped with data collection and establishing the original database. Vanessa El-Achi analysed the data and wrote the manuscript. Bradley de Vries performed the statistical analyses. All authors were involved in editing the manuscript.

## References


1 Lee T, Silver H. Etiology and epidemiology of preterm premature rupture of the membranes. Clin Perinatol. 2001 Dec;28(4):721–34.
2 Simhan HN, Canavan TP. Preterm premature rupture of membranes: diagnosis, evaluation and management strategies. BJOG. 2005 Mar;112(1 Suppl 1):32–7.
3 Mercer BM. Preterm premature rupture of the membranes. Glob Libr Women's Med. 2008. https://doi.org/10.3843/GLOWM.10120.
4 Maxwell GL. Preterm premature rupture of membranes. Obstet Gynecol Surv. 1993 Aug;48(8):576–83.
5 Arias F, Tomich P. Etiology and outcome of low birth weight and preterm infants. Obstet Gynecol. 1982 Sep;60(3):277–81.
6 Kamath-Rayne BD, DeFranco EA, Chung E, Chen A. Subtypes of preterm birth and the risk of postneonatal death. J Pediatr. 2013 Jan;162(1):28–34.e2.
7 Verspyck E, Bisson V, Roman H, Marret S. Adverse respiratory outcome after premature rupture of membranes before viability. Acta Paediatr. 2014 Mar;103(3):256–61.
8 Levine CD. Premature rupture of the membranes and sepsis in preterm neonates. Nurs Res. 1991 Jan-Feb;40(1):36–41.
9 Beaino G, Khoshnood B, Kaminski M, Pierrat V, Marret S, Matis J, et al.; EPIPAGE Study Group. Predictors of cerebral palsy in very preterm infants: the EPIPAGE prospective population-based cohort study. Dev Med Child Neurol. 2010 Jun;52(6):e119–25.
10 Kilbride HW, Thibeault DW. Neonatal complications of preterm premature rupture of membranes. Pathophysiology and management. Clin Perinatol. 2001 Dec;28(4):761–85.
11 Stramrood CA, Wessel I, Doornbos B, Aarnoudse JG, van den Berg PP, Schultz WC, et al. Posttraumatic stress disorder following preeclampsia and PPROM: a prospective study with 15 months follow-up. Reprod Sci. 2011 Jul;18(7):645–53.
12 Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008 Jan;371(9606):75–84.
13 Evaldson G, Lagrelius A, Winiarski J. Premature rupture of the membranes. Acta Obstet Gynecol Scand. 1980;59(5):385–93.
14 Mercer BM, Goldenberg RL, Meis PJ, Moawad AH, Shellhaas C, Das A, et al.; The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The Preterm Prediction Study: prediction of preterm premature rupture of membranes through clinical findings and ancillary testing. Am J Obstet Gynecol. 2000 Sep;183(3):738–45.
15 Ekwo EE, Gosselink CA, Woolson R, Moawad A. Risks for premature rupture of amniotic membranes. Int J Epidemiol. 1993 Jun;22(3):495–503.
16 Waters TP, Mercer B. Preterm PROM: prediction, prevention, principles. Clin Obstet Gynecol. 2011 Jun;54(2):307–12.
17 Harger JH, Hsing AW, Tuomala RE, Gibbs RS, Mead PB, Eschenbach DA, et al. Risk factors for preterm premature rupture of fetal membranes: a multicenter case-control study. Am J Obstet Gynecol. 1990 Jul;163(1 Pt 1):130–7.
18 Auger N, Le TU, Park AL, Luo ZC. Association between maternal comorbidity and preterm birth by severity and clinical subtype: retrospective cohort study. BMC Pregnancy Childbirth. 2011 Oct;11(1):67.
19 Nohr EA, Bech BH, Vaeth M, Rasmussen KM, Henriksen TB, Olsen J. Obesity, gestational weight gain and preterm birth: a study within the Danish National Birth Cohort. Paediatr Perinat Epidemiol. 2007 Jan;21(1):5–14.
20 Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. BJOG. 2007 Feb;114(2):165–9.
21 Moghaddam Banaem L, Mohamadi B, Asghari Jaafarabadi M, Aliyan Moghadam N. Maternal serum C-reactive protein in early pregnancy and occurrence of preterm premature rupture of membranes and preterm birth. J Obstet Gynaecol Res. 2012 May;38(5):780–6.
22 Morgan TK. Role of the Placenta in Preterm Birth: A Review. Am J Perinatol. 2016 Feb;33(3):258–66.
23 Allshouse AA, Jessel RH, Heyborne KD. The impact of low-dose aspirin on preterm birth: secondary analysis of a randomized controlled trial. J Perinatol. 2016 Jun;36(6):427–31.
24 Ghomian N, Hafizi L, Takhti Z. The role of vitamin C in prevention of preterm premature rupture of membranes. Iran Red Crescent Med J. 2013 Feb;15(2):113–6.
25 Roberge S, Villa P, Nicolaides K, Giguère Y, Vainio M, Bakthi A, et al. Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis. Fetal Diagn Ther. 2012;31(3):141–6.
26 van Vliet EO, Askie LA, Mol BW, Oudijk MA. Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth: A Systematic Review and Meta-analysis. Obstet Gynecol. 2017 Feb;129(2):327–36.
27 Waters TP, Mercer B. Preterm PROM: prediction, prevention, principles. Clin Obstet Gynecol. 2011 Jun;54(2):307–12.
28 Park FJ, Leung CH, Poon LC, Williams PF, Rothwell SJ, Hyett JA. Clinical evaluation of a first trimester algorithm predicting the risk of hypertensive disease of pregnancy. Aust N Z J Obstet Gynaecol. 2013 Dec;53(6):532–9.
29 El-Achi V, Park F, O'Brien C, Tooher J, Hyett J. Does low dose aspirin prescribed for risk of early onset preeclampsia reduce the prevalence of preterm prelabor rupture of membranes? J Matern Fetal Neonatal Med. 2019 May;8:1–6.
30 Ip M, Peyman E, Lohsoonthorn V, Williams MA. A case-control study of preterm delivery risk factors according to clinical subtypes and severity. J Obstet Gynaecol Res. 2010 Feb;36(1):34–44.
31 She BQ, Chen SC, Lee FK, Cheong ML, Tsai MS. Low maternal serum levels of pregnancy-associated plasma protein-A during the first trimester are associated with subsequent preterm delivery with preterm premature rupture of membranes. Taiwan J Obstet Gynecol. 2007 Sep;46(3):242–7.
32 Gagnon A, Wilson RD; SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA GENETICS COMMITTEE. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can. 2008 Oct;30(10):918–32.
33 Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al.; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. Am J Obstet Gynecol. 1999 Nov;181(5 Pt 1):1216–21.