

Evaluation of the impact of residual anhydramnios following preterm premature rupture of membranes on respiratory distress syndrome

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Abstract

Objective: The aim of the present study was to evaluate the impact of residual anhydramnios following preterm premature rupture of membranes (PPROM) on respiratory distress syndrome (RDS) after the pregnancy was expectantly managed.

Methods: This study was retrospectively conducted at Erciyes University Medical School, Turkey. It assessed women with singleton pregnancies admitted to the hospital between 2010 and 2020 for expectant management of PPRM between 24th and 28th gestational weeks. The patients were divided into three groups as follows: (1) anhydramnios, (2) oligohydramnios, (3) normal amniotic fluid volume (AFV). Main outcome measure was as follows: The first evaluation was AFV at admission and the primary outcome was a neonatal RDS. Adjusted odds ratios (aOR) and 95% confidence interval (CI) for RDS were calculated for each AFV-at-presentation adjusting for gestational age (GA) at PPRM, GA at delivery, latency period, birth-weight percentile, cesarean birth, and chorioamnionitis.

Results: Of the 440 women with PPRM, 261 fulfilled the inclusion criteria. There were 125 (47.8%) with normal AFV, 71 (27.3%) with oligohydramnios, and 65 (24.9%) with anhydramnios at admission. The maternal demographic characteristics were similar among the groups. Birth weight was significantly different among the groups. RDS was highest in the anhydramnios group (64.6%). Decreased AFV was not associated with RDS in either oligohydramnios or anhydramnios at presentation. A GA at PPRM, latency period >30 days, and cesarean delivery were co-factors in the outcome.

Conclusion: Our results indicated that oligohydramnios and anhydramnios were not associated with RDS risk, but GA at PPRM and delivery, latency period, and cesarean delivery were independently associated with the RDS risk.

Keywords: Preterm premature rupture of membranes, amniotic fluid volume, residual anhydramnios, respiratory distress syndrome.

Özet: Preterm erken membran rüptürü sonrası rezidüel anhidramniyozun respiratuvar distres sendromu üzerindeki etkisinin değerlendirilmesi

Amaç: Çalışmamızın amacı, gebeliğin yakın izlem şeklinde yönetilmesinden sonra preterm erken membran rüptürü sonrası rezidüel anhidramniyozun respiratuvar distres sendromu (RDS) üzerindeki etkisini değerlendirmektir.

Yöntem: Bu çalışma, Erciyes Üniversitesi Tıp Fakültesinde retrospektif olarak gerçekleştirildi. Çalışmada, gebeliğin 24 ile 28. haftaları arasında yakın izlem PEMR yönetimi için 2010 ile 2020 yılları arasında hastaneye başvuran tekil gebelik olguları değerlendirildi. Hastalar şu üç gruba ayrıldı: (1) anhidramniyoz, (2) oligohidramniyoz, (3) normal amniyotik sıvı hacmi (ASH). Ana sonuç ölçümleri İlk değerlendirme başvurusundaki ASH iken birincil sonuç neonatal RDS idi. RDS için düzeltilmiş olasılık oranları (aOR) ve %95 güven aralığı (GA); PEMR’de gestasyonel yaş (GY), doğumda GY, gecikme dönemi, doğum ağırlığı persantili, sezaryen doğum ve koryoamniyonit bakımından düzeltilen her bir başvurudaki ASH için hesaplandı.

Bulgular: PEMR’li 440 kadının 261’i çalışmaya dahil olma kriterlerini karşıladı. Başvuruda normal ASH’li 125 (%47.8) olgu, oligohidramniyozlu 71 (%27.3) olgu ve anhidramniyozlu 65 (%24.9) olgu vardı. Maternal demografik özellikler, gruplar arasında benzerdi. Doğum ağırlığı, gruplar arasında anlamlı şekilde farklıydı. RDS, anhidramniyoz grubunda en yüksek seviyedeydi (%64.6). Azalmış ASH, başvuruda oligohidramniyoz veya anhidramniyoz grubunda RDS ile ilişkili değildi. PEMR’de GY, 30 günden büyük gecikme dönemi ve sezaryen doğum, sonuçta ortak faktörlerdi.

Sonuç: Sonuçlarımız, oligohidramniyoz ve anhidramniyozun RDS riskiyle ilişkili olmadığını, fakat PEMR ve doğumda GY’nin, gecikme döneminin ve sezaryen doğumun bağımsız olarak RDS riskiyle ilişkili olduğunu göstermektedir.

Anahtar sözcükler: Preterm erken membran rüptürü, amniyotik sıvı hacmi, rezidüel anhidramniyoz, respiratuvar distres sendromu.

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Introduction

Preterm premature rupture of membranes (PPROM), defined as fetal membrane rupture without signs of labor <37 weeks gestation, seriously complicates 3–4% of all pregnancies and is a major risk for perinatal morbidity and mortality. Fetal death from PPRM may occur mainly due to reasons such as preterm birth, anhydramnios, umbilical cord compression, prolapsed umbilical cord, perinatal infection and abruptio placentae.^[1–4] Amniotic fluid is required for normal fetal development and growth.^[5] Fetal pulmonary development depends on sufficient amniotic fluid; hence severe oligohydramnios during pregnancy can cause pulmonary hypoplasia.^[6,7] Pulmonary hypoplasia is mainly associated with severe oligohydramnios <22 weeks gestation.^[6,8,9]

Respiratory distress syndrome (RDS) is a widespread and life-threatening disease of neonates and a major cause of morbidity and mortality in premature infants.^[10] Surfactant is a liquid made by the lungs of an unborn baby beginning at ~26 gestational weeks that keeps the airways open and allows a baby to breathe in air after delivery. When there is a surfactant deficiency, RDS develops and can lead to abnormal respiratory function as the baby proceeds to neonatal life,^[10] hence, it is critical that this condition be determined early in the pregnancy.^[11] The aim of the present study was to evaluate the impact of residual oligohydramnios and anhydramnios after PPRM on RDS even when the pregnancy was expectantly managed.

Methods

This study was retrospectively conducted at Erciyes University Medical School, Turkey, and approved by the ethics committee of the university (2019/51); it was conducted in accordance with the Declaration of Helsinki. The present study assessed women with a singleton pregnancy admitted to Erciyes University Medicine School with PPRM at 24+0 to 28+6 weeks of gestation between January 1, 2010 and June 1, 2020, and who had undergone expectant management. We wanted to evaluate impact of long-term latency period (>20 days) on RDS, hence; pregnant women with PPRM at 24th to 29th weeks of gestation were included to the study. The exclusion criteria were as follows: (1) necessity of immediate delivery, (2) multifetal gestations, (3) cases with missing data, (4) major fetal anomaly, (5) chronic hypertension, (6) gestational

hypertension, (7) preeclampsia, (8) intrauterine growth restriction, (9) collagen vascular disease, (10) gestational diabetes mellitus, (11) types 1 and 2 diabetes, or (12) chronic systemic disease. The flow chart of the study population is illustrated in **Fig. 1**.

We identified the patients diagnosed with PPRM from the hospital's database, subsequently, we examined the demographic characteristics, medical and obstetric history, age of gestation (GA) in diagnosis of PPRM, duration of the latency period, and complications related to pregnancy treatment (e.g. chorioamnionitis, maternal sepsis, or placental abruption). Newborn characteristics were also evaluated for RDS, birth weight, GA at delivery, and Apgar assessment.

Amniotic fluid volume (AFV) was the primary clinical measure of a membrane rupture on presentation to the hospital and the ultrasound examination was conducted that included an estimation of fetal weight and a biophysical profile. During the first clinical examination of those admitted to the clinic with membrane rupture, a four-quadrant technique was used to ultrasonographically measure AFV. An anhydramnios AFI is defined as ≤ 2 cm, oligohydramnios AFI as 2–5 cm, and normal AFI as 8–24 cm.^[12] The PPRM patients studied were divided into the following three groups for assessing residual AFV: (1) anhydramnios, (2) oligohydramnios, and (3) normal AFV.

The primary outcome to be assessed in the present study was neonatal RDS, which was identified by some pediatricians who was blinded to the Doppler evaluations. Other factors in an RDS diagnosis were the existence of diffuse, fine, granular densities and decreased pulmonary volume with a higher oxygen necessity.^[13]

A trained obstetrician diagnosed PPRM after the patient was admitted to the hospital. The presence of amniotic fluid either passing through the cervix or pooling in the uterine fornix indicated PPRM. The nitrazine paper test and a ferning pattern seen on the dried vaginal secretions indicated the presence of amniotic fluid and a ruptured membrane. The date of the beginning of the patient's last menstrual cycle was used to determine her gestational week; if that date was not known, the gestational age was calculated using ultrasonographic measurements taken during the first trimester. The protocol comprised monitoring daily vital signs and uterine tenderness, administered a non-stress test twice/day, assessing the biophysical profile twice/week, and administering 1 g azithromycin orally

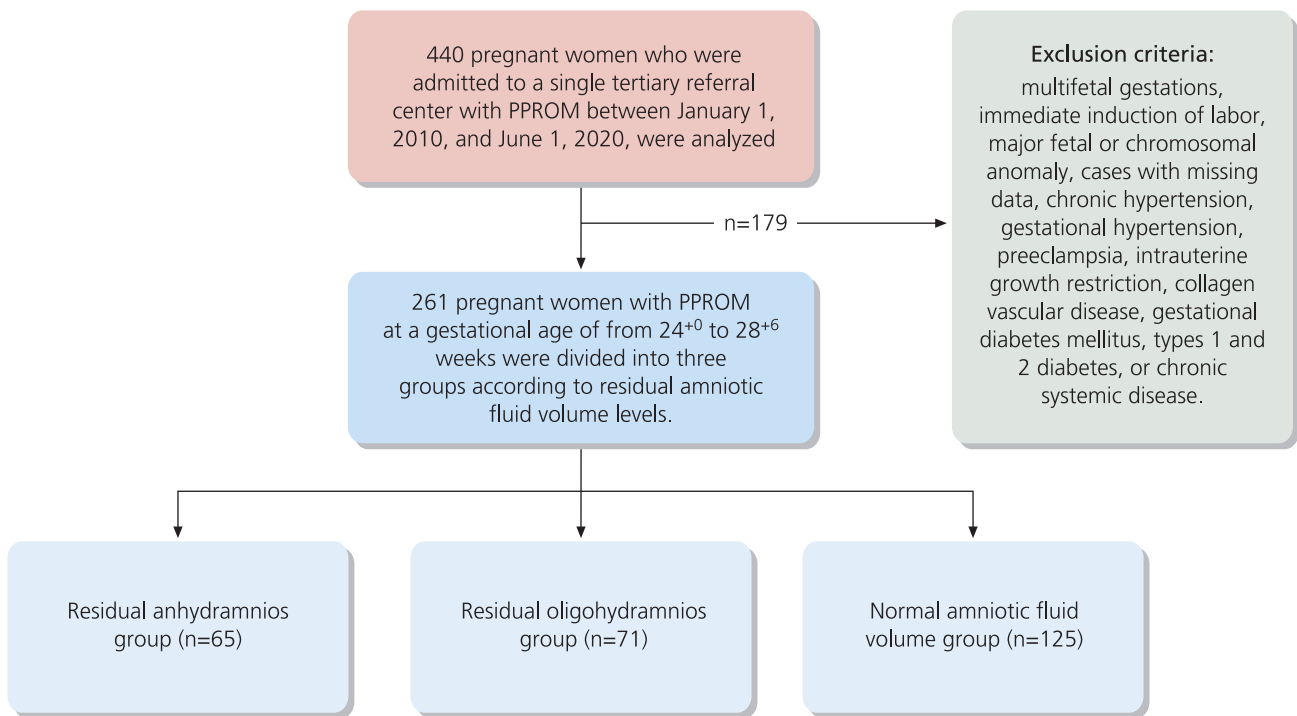


Fig. 1. Flow chart for the study population.

at admission. While hospitalized, 2 g ampicillin was administered intravenously every 6 h for 2 day, followed by 500 mg amoxicillin orally three times/day or 875 mg orally two times/day for an additional 5 day.^[14] Vaginal examinations were refrained during the pregnant woman was asymptomatic. If necessary, a sterile speculum inspection was opted to digital examination. PPROM women with a cervical cerclage were assessed for whether to remove the cerclage.^[15] After the diagnosis of PPROM, two doses of 12 mg betamethasone were administered intramuscularly every 24 hours.^[16] Magnesium sulfate was applied for impact of fetal neuro-protection in women who gave birth at before 32 weeks of gestation.^[17] Women with PPROM who were at risk of intrauterine infection or placental abruption or who had non-reassuring fetal testing or a high risk of cord prolapse were counseled on the preference of an expeditious delivery. If both the mother and the fetus were stable, the pregnancy continued to be managed and delivery was preferred at 34th weeks. A diagnosis of chorioamnionitis was made if the woman had a temperature of $\geq 38.0^{\circ}\text{C}$ without cause not related to the pregnancy, and at least two of the following conditions were

observed: leukocytosis, new-onset foul-smelling vaginal discharge, uterine tenderness, maternal or fetal tachycardia.^[18] In the absence of congenital anomalies, fetal growth restriction (FGR) was diagnosed according to Delphi consensus criteria.^[19] Maternal sepsis was identified when there were symptoms belong to end-organ dysfunction such as hypotension, oliguria, high creatinine, diffuse intravascular coagulation, or respiratory failure in the presence of maternal infection such as tachycardia, positive blood cultures and fever. Placental abruption was diagnosed based mainly on evidence of new onset vaginal bleeding, recurring painful contractions, and bloody amniotic fluid or blood clots in the placenta during birth.

Statistical analyses were conducted using SPSS version 20.0 (IBM Inc., Armonk, NY, USA). The Kruskal-Wallis H test was used to test the normality of the data. The Levene test was used to evaluate the assumption of variance homogeneity; values are expressed as the mean \pm standard deviation, median (25th–75th percentile), or n (%). One-way analysis of variance was used to compare multiple groups after evaluating for normal distribution. Multivariate logistic regression analysis was used to

assess the relationship between the AFV at presentation and the primary outcome (the normal AFV group was used as reference), while adjusting for possible confounding factors including chorioamnionitis, GA at PPRM, GA at delivery, latency period, birth weight, and cesarean birth.

Results

Of the 440 women applied with PPRM in the period of study, 261 fulfilled the inclusion criteria (see **Fig. 1**; flow chart). There were 125 (47.8%) patient with normal AFV, 71 (27.3%) with oligohydramnios, and 65 (24.9%) with anhydramnios at admission. Demographic features of the all study patients according to AFV at admission are showed in **Table 1**. Maternal age, nulliparity, body mass index, ethnicity, and previous cesarean delivery were similar among the groups ($p=0.330$, $p=0.680$, $p=0.320$, $p=0.650$, and $p=0.580$, respectively).

Maternal and newborn outcomes in all study groups are showed in **Table 2**. Birth at a GA earlier than that in the normal AFV and oligohydramnios groups ($p<0.001$) was primarily a result of the differences in the time of the latency period; this period was lower in anhydramnios group than in the others ($p<0.001$). There were no significant differences among the groups in terms of cesarean delivery, chorioamnionitis, maternal sepsis, placental abruption, or cord prolapse ($p=0.920$, $p=0.480$, $p=0.240$, $p=0.870$, and $p=0.470$, respectively). The rate of RDS was 64.6% in the anhydramnios group, 39.4% in the oligohydramnios group and 26.4% in the normal-AFV group. The rate of RDS was the greatest in the anhydramnios group ($p<0.001$) (**Table 2**). Birth weight was 1488 ± 208 g in anhydramnios group, 1716 ± 183 g in oligohydramnios group, and 2002 ± 159 g in normal-AFV group, a significant difference among the groups ($p<0.001$). There were no significant differences among the groups with regard to birth weight percentile, umbil-

ical cord pH <7.20 , and 5-minute Apgar score <7 ($p=0.740$, $p=0.220$, and $p=0.360$, respectively).

When the normal-AFV group was used as the reference, a multivariate logistic regression analysis was used to assess the relationship between the AFV at admission and the primary outcome; the data were adjusted for possible confounding factors, such as GA at PPRM, GA at delivery, latency period >30 d, birth-weight percentile, cesarean delivery, and chorioamnionitis. After adjusting for the variables, we observed that a decreased AFV was not associated with RDS for both oligohydramnios (adjusted odds ratio [AOR], 4.42; 95% confidence interval [CI], 0.21–07.30) and anhydramnios (AOR, 7.83; 95% CI, 0.54–77.45) at presentation (**Table 3**). Other factors that were independently related to the primary outcome were GA at PPRM (AOR, 0.38; 95% CI, 0.17–0.86), GA at delivery (AOR, 0.14; 95% CI, 0.04–0.54), latency period >30 d (AOR, 0.18; 95% CI, 0.05–0.54), and cesarean birth (AOR, 2.66; 95% CI, 1.25–5.68).

Discussion

Respiratory distress syndrome continues to be a common and life-threatening disease in neonates, particularly in preterm neonates. The aim of the present study was to evaluate the impact of residual oligohydramnios and anhydramnios after PPRM on RDS when the pregnancy was expectantly managed. The results of our assessments were that (1) approximately one-half of the women with early PPRM presented with oligohydramnios, with 24.9% of them presenting with residual anhydramnios; (2) oligohydramnios and anhydramnios at presentation were not associated with the risk of RDS after adjusting for the variables using multivariate logistic regression analysis; and (3) GA at PPRM, GA at delivery, latency period, and cesarean delivery were independently associated with RDS risk.

Table 1. Comparison of maternal physical characteristics among groups.

Characteristic	Anhydramnios (n=65)	Oligohydramnios (n=71)	Normal amniotic fluid volume (n=125)	p-value*
Maternal age (years)	33.4 \pm 5.1	31.6 \pm 5.9	31.6 \pm 5.7	0.330
Nulliparity	20 (30.7)	22 (30.9)	41 (32.8)	0.680
Body mass index (kg/m ²)	29.5 \pm 1.1	29.0 \pm 1.3	29.3 \pm 1.5	0.320
Ethnicity (Caucasian)	62 (95.3)	68 (95.7)	121 (96.8)	0.650
Previous cesarean history	23 (34.3)	25 (35.2)	40 (32)	0.580

The values were presented the mean \pm SD or n (%). *All comparisons were made by ANOVA test.

Table 2. Comparison of perinatal outcomes and respiratory distress syndrome rates among groups.

Outcomes	Anhydramnios (n=65)	Oligohydramnios (n=71)	Normal amniotic fluid volume (n=125)	p-value*
Gestational age at PPROM (week)	26.9±1.0	27.0±0.8	27.0±0.8	0.626
Gestational age at delivery (week)	29.9±1.8 ^A	31.4±1.9 ^B	32.6±1.4 ^C	<0.001
Latency period (day)	18.5±4.8 ^D	26.2±7.2 ^E	33.2±6.2 ^F	<0.001
Cesarean delivery	35 (53)	39 (55)	71 (57)	0.920
Chorioamnionitis	11 (17)	15 (21.1)	18 (14.4)	0.480
Maternal sepsis	2 (3.1)	1 (1.4)	1 (0.8)	0.240
Placental abruption	3 (4.6)	3 (4.2)	4 (3.2)	0.870
Cord prolapsed	3 (4.6)	2 (2.8)	2 (1.6)	0.470
Birth weight (g)	1488±208 ^G	1716±183 ^H	2002±159 ^I	<0.001
Birth weight percentile	56±14.4	58±17.1	61±18.6	0.740
Umbilical cord pH <7.20	4 (6.2)	2 (2.8)	2 (1.6)	0.220
5-minute Apgar score <7	5 (7.7)	3 (4.2)	4 (3.2)	0.360
Respiratory distress syndrome	42 (64.6) ^J	28 (39.4) ^K	33 (26.4) ^L	<0.001

The values are presented the mean ± SD or n (%). *All comparisons were made by ANOVA test. PPROM: preterm premature rupture of membranes. ^A vs ^B - significant, ^B vs ^C - significant, ^A vs ^C - significant; ^D vs ^E - significant, ^E vs ^F - significant, ^D vs ^F - significant; ^G vs ^H - significant, ^H vs ^I - significant, ^G vs ^I - significant; ^J vs ^K - significant, ^K vs ^L - not significant, ^J vs ^L - significant.

The results of studies on the association between oligohydramnios and poor newborn outcomes in PPROM women are contradictory due to the differences in the inclusion criteria used and the targeted primary results. Some trials did not concentrate about newborn respiratory morbidity as a primary outcome; therefore, the description of respiratory morbidity is not as clear as in our trial.^[1,20-23] In addition, the results of most of the studies were not classified considering to the oligohydramnios severity at admission.^[1,7,20-24] Two recent studies aimed to clarify the relationship between residual AFV and respiratory morbidity between 20th and 29th gesta-

tional weeks. In their well-designed, large, retrospective study using singleton pregnancies for expectant PPROM management at 20+0 to 28+6 weeks gestation, Weiner et al.^[25] declared that oligohydramnios and severe oligohydramnios at admission are independently related to severe respiratory morbidity, which they described as one of the following: (1) the demand for respiratory assistance and surfactant in the condition of mechanical ventilation applying an endo-tracheal tube for ≥3 days; (2) bronchopulmonary dysplasia described as oxygen demand at 36 weeks gestation or when transferred to a level-II facility. Mousavi et al.^[24] have found no statistically significant

Table 3. Logistic regression analysis of associations between delivery characteristics and respiratory distress syndrome in pregnancies complicated by preterm premature rupture of the membrane.

Respiratory distress syndrome	Odds ratio (95%CI)	p-value	Adjusted odds ratio (95%CI)	Adjusted p-value
Normal AFV at presentation	Reference		Reference	
Gestational age at PPROM	0.61 (0.41–0.90)	0.18	0.38 (0.17–0.86)	0.019
Gestational age at delivery	0.13 (0.05–0.30)	<0.001	0.14 (0.04–0.54)	0.004
Latency period	0.06 (0.02–0.16)	<0.001	0.18 (0.05–0.54)	0.002
Cesarean delivery	2.22 (1.18–4.45)	0.010	2.66 (1.25–5.68)	0.011
Chorioamnionitis	2.84 (1.45–5.48)	0.002	0.28 (0.07–1.06)	0.060
Birth weight percentile	0.76 (0.34–1.67)	0.522	2.05 (0.57–7.40)	0.272
Oligohydramnios at presentation	1.32 (0.30–5.73)	0.720	4.42 (0.21–7.30)	0.324
Anhydramnios at presentation	25.48 (9.65–67.30)	<0.001	7.83 (0.54–77.45)	0.993

AFV: amniotic fluid volume; CI: confidence interval; PPROM: preterm premature rupture of membrane.

differences among gestational age at presentation, latency period, gestational age at birth, and RDS rates in PPROM pregnancies at a GA of 26th–29th weeks.

In the present study, after conducting a multivariate logistic regression analysis to evaluate the relationship between the AFV at admission and the primary outcome and while adjusting for important possible confounding factors such as GA at PPROM, GA at delivery, latency period, birth weight percentile, cesarean delivery, and chorioamnionitis, we observed that neither oligohydramnios nor anhydramnios at admission with PPROM was related to RDS risk. In addition, we found that, consistent with the data in the current literature, anhydramnios at presentation is associated with a decreased latency period, GA at delivery, and low birth weight.^[1,26–28] Our results can be explained by the data having been adjusted for potential important confounding variables. It is well documented in the literature that consistent with our results, prematurity, low birth weight, and cesarean delivery are major RDS risk factors.^[29,30] We know that the primary cause of RDS is a deficiency in pulmonary surfactant, which is developmentally regulated in the preterm infant. In that infant, a decrease in both the quantity and quality of surfactant contributes to decreased surfactant activity, which results in RDS. Inadequate surfactant activity in the developing lungs results in high surface tension, which leads to lung instability at end expiration, low lung volume, and decreased compliance. Surfactant deficiency also leads to lung inflammation and respiratory epithelial injury, possibly causing pulmonary edema and increased airway resistance.

The retrospective nature of our study had some limitations. We recognized that AFV is dynamic and changes consistently; however, the groups we assessed were described by AFV at admission, without considering the AFV changes pending the latency period. Still, we suggest that AFV is more beneficial for clinical management in admission, because the longitudinal AFV levels are unknown during evaluation. The principal power of the present research were the relatively wide cohort, having the study patients in a single center and managing them considering to a uniformed protocol, adjusting the findings for possible confounding factors, and having a relatively homogeneous cohort that was limited to events of PPROM between 24th and 28th gestational weeks.

Conclusion

Our results indicated that neither oligohydramnios nor anhydramnios during admission was related to the RDS

risk, but that GA at PPROM, GA at delivery, latency period, and cesarean delivery are independently associated with that risk. This knowledge can be taken into account while advising to a pregnant woman with early PPROM about newborn outcome and management choices.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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