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The association of the amniotic fluid index (AFI) with perinatal fetal and maternal outcomes in pregnancies complicated by preterm premature rupture of membranes (PPROM)

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ABSTRACT

Objectives: To investigate association of amniotic fluid index (AFI) with perinatal fetal and maternal outcomes in pregnancies complicated by preterm premature rupture of membranes (PPROM)

Material and methods: A total of 70 singleton pregnancies complicated by PPROM at 23–33 weeks' gestation were enrolled in this prospective observational study. Data on maternal clinical and obstetric characteristics [maternal age, gravidity, parity, PPROM time, and AFI (cm), latency period, treatments, type of delivery, length of hospital stay (LOS, day)], fetal characteristics (gestational age at delivery, birth weight (g), gender) and maternal and fetal complications were recorded and compared in AFI < 5 cm (n = 27) and AFI ≥ 5 cm (n = 21) groups.

Results: Overall AFI was ≤ 5 cm in 27 (56.3%) patients and > 5 cm in 21 (43.7%) patients. No significant difference was noted in maternal clinical and obstetric characteristics, gestational age at delivery and gender of the newborn as well as in maternal and fetal complications rates with respect to AFI groups. AFI was correlated positively with latency period (r = 0.399, p = 0.018) and negatively with postpartum LOS (r = –0.314, p = 0.030).

Conclusions: In conclusion, our findings seems to indicate increased likelihood of shorter latency to delivery and longer postpartum LOS with decrease in AFI after PPROM between 23–33 weeks' gestation, whereas no impact of AFI on mode of delivery and fetal or maternal complications.

Key words: Preterm premature rupture of membranes; amniotic fluid index; fetal outcomes; maternal outcomes

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INTRODUCTION

Premature rupture of fetal membranes (PROM), the leakage of amniotic fluid prior to labour irrespective of gestational age, occurs in 2–25% of all pregnancies, while PROM before 37 weeks of gestation occurs in nearly 3% of all pregnancies and referred to as preterm PROM (PPROM) [1–4].

Early recognition and appropriate treatment of PPROM is crucial for preventing potential adverse perinatal outcomes related to prematurity (*i.e.* neonatal morbidity and mortality) and for minimizing the risk of fetal and maternal complications [3–6]. However, PPROM continues to be a challenging condition in current obstetric practice in terms of controversies regarding the optimal timing and route of delivery to minimize maternal and perinatal morbidity [3, 5].

Amniotic fluid index (AFI), a widely used method for evaluation of fetal well–being, is considered a useful parameter in this regard, given its potential in predicting adverse outcomes, aiding to decide on optimal mode of delivery in pregnancies complicated by PPROM [5, 7, 8]. Accordingly, presence of oligohydramnios (AFI < 5 cm) after PPROM has been suggested to be associated with increased likelihood of adverse fetal (*i.e.* intrauterine growth restriction, fetal distress, pulmonary hypoplasia, respiratory distress syndrome, neonatal sepsis, necrotizing enterocolitis, intraventricular hemorrhage, and bronchopulmonary dysplasia) and maternal (*i.e.* chorioamnionitis) perinatal outcomes, contributing to an increase in neonatal sepsis and mortality [5, 8–12].

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However, the utility of AFI after PPROM in terms of adverse perinatal outcomes has not been extensively studied along with considerable controversy among the published studies [5, 8, 9, 12–16].

This study was therefore was designed to investigate the potential association of AFI with fetal/maternal perinatal adverse outcomes in pregnancies complicated by PPROM.

MATERIALS AND METHODS

Study population

A total of 70 singleton pregnancies complicated by PPROM at 23–33 weeks' gestation were enrolled in this prospective observational study conducted at a single tertiary care center between September 2018 and September 2019. Women with singleton, non–anomalous fetuses with suspected diagnosis of PPROM at 23–33 weeks' gestation and amniotic fluid volume assessment at the time of presentation were included in the study. Presence of multiple pregnancy, cerclage major congenital anomaly, oligohydramnios, polyhydramnios, pregnancy-related hypertensive disorder, cervical dilatation ≥ 6 cm on admission and delivery within 2 hours of membrane rupture were the exclusion criteria of the study. Accordingly, final study population subjected to analysis was composed of 48 pregnant women due to exclusion of 22 women due to lack of PPROM diagnosis (n = 13), multiple pregnancy (n = 2), cervical dilatation ≥ 6 cm (n = 2), hypertensive disease (n = 1), cerclage (n = 1), lumbar meningomyelocele (n = 1), idiopathic polyhydramnios (n = 1) and discharge at her own request (n = 1) (Fig. 1).

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

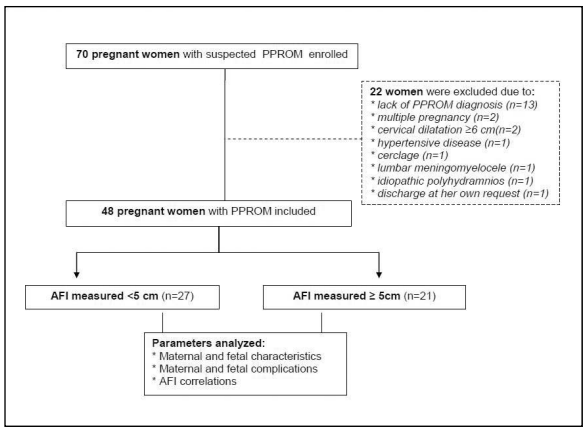

Figure 1. Study flow chart

Assessments

Data on maternal clinical and obstetric characteristics [maternal age, gravidity, parity, body mass index prior to pregnancy (kg/m^2), smoking status, PPROM time, amniotic fluid appearance and AFI (cm), latency period (days from rupture of amniotic sac to the delivery), treatments (steroid, magnesium), type of delivery, length of hospital stay (LOS, day)], fetal characteristics (gestational age at delivery, birth weight (g), gender) and maternal complications (placental abruption, retention, endometritis, bleeding, chorioamnionitis, last CRP before delivery, WBC and body temperature) and fetal complications within the first month of post-natal life (ICU stay, sepsis, meconium aspiration, respiratory distress syndrome, grade 3–4 intraventricular hemorrhage, umbilical artery pH level and 5th min Apgar score) were recorded. Patients were categorized into 2 groups on the basis of a 4-quadrant AFI < 5 cm (n = 27) or ≥ 5 cm (n = 21), while maternal and fetal characteristics and complications were evaluated with respect to AFI groups and correlation of AFI with other study parameters was analyzed.

PPROM diagnosis

PPROM diagnosis was based on patient history and physical examination findings including presence of typical gross amniotic fluid leakage history and/or identification of pooling of amniotic fluid in the posterior vaginal vault on sterile speculum examination. In women with suspected anamnesis but without history of gross leakage or positive findings on speculum examination, the diagnosis was made by positivity of placental alpha microglobulin–1 test (Amnisure ROM Test®, QIAGEN, USA) in the vaginal fluid. The pregnant women were monitored daily by clinical and obstetric examination, as well as with bacteriology smears and periodic hemogram analysis for screening of infections.

Calculation of amniotic fluid index (AFI)

AFI was measured ultrasonographically with 4–8 MHz transabdominal convex probe General Electric Voluson (GE Healthcare, Chicago, IL, United States) device and calculated by four quadrant technique, which is sum of the deepest vertical length of pocket of fluid in each quadrant without umbilical cord [17].

Treatments

All pregnant women received a single course of betamethasone, consisting of two 12–mg injections during the first 24 hours after admission to induce fetal lung maturation and antibiotic treatment including single dose oral azithromycin (1 g) and *i.v.* ampicillin (4 × 2 g) within the first 48–h, as followed by oral amoxicillin (3 × 500 mg) to complete the 7–day antibiotherapy [1]. In women with delivery expected to occur before 32nd gestational week, magnesium sulphate

prophylaxis was administered for fetal neuroprotection (a loading dose of 6 g infused for 20–30 minutes followed by a maintenance infusion of 2 g per hour).

Emergency C/S was performed in women with placental abruption and identification of decelerations indicating fetal distress during NST. The decelerations were interpreted in accordance with ACOG Bulletin description.

Fetal and maternal complications

Fetal and maternal complications were recorded up to 1 month postpartum. Respiratory distress syndrome was defined as a requirement for supplemental oxygen for more than 48 hours with a reticulogranular appearance on chest X–ray. Neonatal sepsis was diagnosed either by positive blood culture or by a combination of clinical signs and laboratory findings, such as leukopenia, thrombocytopenia, and elevated CRP levels. ICU need was considered for at least 24 hours of ICU stay in the neonatal period.

Chorioamnionitis was diagnosed based on increased body temperature (> 38 °C) accompanied with positivity of at least one of the followings: lower abdominal or uterine tenderness, malodorous amniotic discharge, persistent fetal tachycardia or positive laboratory findings (CRP > 0.5 mg/dL or WBC > 20.000) [18]. Postpartum endometritis was diagnosed based on increased body temperature (> 38 °C) and uterine tenderness and exclusion of other infection foci. Postpartum bleeding was considered in bleedings that cause 10% decline in hematocrit levels or necessitate blood transfusion.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Pearson Chi-Square test (Exact), Fisher Exact test (Exact), Fisher Freeman Halton Test (Monte Carlo) were used to analyze categorical data, while numerical data were analyzed with independent samples-t test (Bootstrap) and Mann Whitney U test (Monte Carlo). Correlation analysis was performed with Spearman's rho test. ROC curve was plotted to determine the role of AFI in predicting fetal birth weight with calculation of area under curve (AUC) and cut-off value via ROC analysis. Data were expressed as median (min–max), 95% confidence interval (CI) and n (%) where appropriate $p < 0.05$ was considered statistically significant.

RESULTS

Overall, mean ± SD maternal age was 27.15 ± 5.04 years, 54.2% of women were multiparous women. Mean PPROM time was 29.11 (SD 2.22) weeks, while spontaneous vaginal delivery was noted in 81.3% of women. Overall mean ± SD AFI was 4.41 ± 1.80 cm, while AFI was ≤ 5 cm in 27 (56.3%) patients and > 5 cm in 21 (43.7%) patients. Median latency period was 8 days (range, 1 to 26 days), while length of postpartum LOS was 2.5 days (range, 1 to 7 days) (Tab. 1).

No significant difference was noted in maternal clinical and obstetric characteristics, gestational age at delivery and gender of the newborn with respect to AFI groups. Latency period and LOS were also similar between AFI < 5 cm and ≥ 5cm groups (Tab. 1).

Fetal birth weight was significantly higher in the AFI ≥ 5 cm group as compared with AFI < 5 cm group (1622.86 ± 273.75 vs 1440.74 ± 336.33, $p = 0.042$) (Tab. 1).

Maternal and fetal complications

Overall, maternal complications were observed in 41.7% of women, including chorioamnionitis (33.3%) and endometritis (25.0%) in most of women (Tab. 2).

Overall, fetal complications were observed in 72.9% of neonates, including 5–min Apgar score ≤ 5 (52.1%), ICU stay (66.7%), and respiratory distress syndrome (52.1%) in most of neonates (Tab. 3).

No significant difference was noted in presence, type and number of maternal and fetal complications with respect to AFI groups (Tab. 3).

Correlation of AFI with other study parameters

AFI was correlated positively with latency period ($r = 0.399$, $p = 0.018$) and negatively with postpartum LOS ($r = –0.314$, $p = 0.030$). No correlation of AFI was noted with maternal age, PPROM time, delivery week or number of maternal and fetal complications (Tab. 4).

DISCUSSION

Our findings revealed positive correlation of AFI with latency period and association of AFI < 5 cm after PPROM with higher postpartum LOS in pregnancies complicated by PPROM at 23–33 weeks' gestation, whereas no significant difference was noted in fetal and maternal complication rates and mode of delivery with respect to AFI groups (< 5 cm vs ≥ 5 cm).

Increased likelihood of shorter latency to delivery with decreasing AFI values after PPROM in the current study supports the data on association of lower (< 5 cm) AFI values with shorter latency to delivery reported from a prospective analysis of 225 singleton pregnancies complicated by PPROM between 24 and 32 weeks' gestation [12] as well as in a retrospective analysis of 389 women with PPROM between 24 and 34 weeks of gestation [14]. However, in both studies, authors also reported association of oligohydramnios after PPROM with higher rate of cesarean delivery [12, 14] and perinatal adverse outcomes such as early–onset neonatal sepsis [12] and chorioamnionitis [12, 14]. In this regard, the wide range of latency period length (1–26 days) in the current study should also be noted given that this alone may also refer to a considerable risk factor of adverse outcome.

Table 1. Maternal and fetal characteristics with respect to AFI

Maternal characteristics		Total (n = 48)	AFI < 5 cm (n = 27)	AFI ≥ 5 cm (n = 21)	P
Maternal age, Mean ± SD		27.15 ± 5.04	27.15 ± 5.19	27.14 ± 4.97	0.997[t]
Gravidity, Median (Min/Max)		2 (1/5)	2 (1/5)	2 (1/4)	0.402[u]
Parity, n (%)					
	Primipar	22 (45.8)	12 (44.4)	10 (47.6)	0.999[p]
	Multipar	26 (54.2)	15 (55.6)	11 (52.4)	
BMI [kg/m^2], n (%)					
	< 18.5	9 (18.8)	4 (14.8)	5 (23.8)	0.664[ff]
	18.5–24.9	18 (37.5)	9 (33.3)	9 (42.9)	
	25–29.9	12 (25.0)	8 (29.6)	4 (19.0)	
	> 30	9 (18.8)	6 (22.2)	3 (14.3)	
Smoking, n (%)					
	No	44 (91.7)	24 (88.9)	20 (95.2)	0.621[f]
	Yes	4 (8.3)	3 (11.1)	1 (4.8)	
PPROM time [week], Mean ± SD		29.11 ± 2.22	28.80 ± 2.21	29.51 ± 2.22	0.291[t]
Amniotic fluid, n (%)					
	Clear	44 (91.7)	24 (88.9)	20 (95.2)	0.999[ff]
	Bloody	1 (2.1)	1 (3.7)	0 (0.0)	
	Meconium	3 (6.3)	2 (7.4)	1 (4.8)	
Delivery type, n (%)					
	C/S	9 (18.8)	5 (18.5)	4 (19.0)	0.999[f]
	Vaginal	39 (81.3)	22 (81.5)	17 (81.0)	
AFI, Mean ± SD.		4.41 ± 1.80	3.05 ± 0.97	6.15 ± 0.83	**0.001[t]**
Latency period [day], Median (Min/Max)		8 (1/26)	7 (1/19)	9 (1/26)	0.322[u]
Length of hospital stay [day], Median (Min/Max)		2.5 (1/7)	3 (1/7)	2 (1/7)	0.071[u]
Steroid, n (%)					
	No	1 (2.1)	1 (3.7)	0 (0.0)	–
	Yes	47 (97.9)	26 (96.3)	21 (100.0)	
Magnesium, n (%)					
	No	8 (16.7)	4 (14.8)	4 (19.0)	0.715[f]
	Yes	40 (83.3)	23 (85.2)	17 (81.0)	
Fetal characteristics					
Gestational age at delivery (week), Mean ± SD.		30.31 ± 1.97	29.86 ± 2.02	30.88 ± 1.80	0.078[t]
< 34 weeks		44 (91.7)	25 (92.6)	19 (90.5)	0.999[f]
34 weeks		4 (8.3)	2 (7.4)	2 (9.5)	
Birth weight [g], Mean ± SD.		1520.42 ± 320.62	1440.74 ± 336.33	1622.86 ± 273.75	**0.042[t]**
Gender, n(%)					
	Girl	26 (54.2)	15 (55.6)	11 (52.4)	0.999[p]
	Boy	22 (45.8)	12 (44.4)	10 (47.6)	

[t] — Independent Samples, [t] —Test(Bootstrap), [u] — Mann Whitney U test(Monte Carlo), [p] — Pearson Chi-Square Test(Exact), [f] — Fisher Exact test(Exact), [ff] — Fisher Freeman Halton Test(Monte Carlo), [rc] — Roc Curve Analysis (Youden index J-Honley&Mc Nell), AUC — Area under the ROC curve, SD. — Standard deviation, Med — Median, Min — Minimum, Max — Maximum

In a retrospective study of 191 pregnancies with PPROM, authors reported higher rates of cesarean sections, 5-min Apgar score < 7, chorioamnionitis, respiratory distress syndrome, composite neonatal morbidity and neonatal mortality in the group with an AFI < 5 cm vs those with an AFI > 5 cm [19]. Moreover, in a retrospective cohort study of 86 pregnant women with PPROM at 24 to 35 weeks' gestation, authors reported higher rate of perinatal mortality in

Table 2. Maternal complications with respect to AFI

		Total (n = 48)	AFI < 5 cm (n = 27)	AFI ≥ 5 cm (n = 21)	P
		Med (Min/Max)	Med (Min/Max)	Med (Min/Max)	
Number of complications		0 (0/3)	0 (0/3)	0 (0/3)	0.349[u]
		n (%)	n (%)	n (%)	
Complications					
	Absent	28 (58.3)	14 (51.9)	14 (66.7)	0.382[p]
	Present	20 (41.7)	13 (48.1)	7 (33.3)	
Placental abruption					
	Absent	47 (97.9)	26 (96.3)	21 (100.0)	–
	Present	1 (2.1)	1 (3.7)	0 (0.0)	
Retention					
	Absent	46 (95.8)	26 (96.3)	20 (95.2)	–
	Present	2 (4.2)	1 (3.7)	1 (4.8)	
Endometritis					
	Absent	36 (75.0)	19 (70.4)	17 (81.0)	0.510[p]
	Present	12 (25.0)	8 (29.6)	4 (19.0)	
Bleeding					
	Absent	45 (93.8)	25 (92.6)	20 (95.2)	0.999[f]
	Present	3 (6.3)	2 (7.4)	1 (4.8)	
Chorioamnionitis					
	Absent	32 (66.7)	17 (63.0)	15 (71.4)	0.758[p]
	Present	16 (33.3)	10 (37.0)	6 (28.6)	
CRP					
	normal	36 (75.0)	19 (70.4)	17 (81.0)	0.510[p]
	elevated	12 (25.0)	8 (29.6)	4 (19.0)	
WBC					
	< 21	38 (79.2)	21 (77.8)	17 (81.0)	0.999[f]
	> 21	10 (20.8)	6 (22.2)	4 (19.0)	
Body temperature [°C]					
	< 38	32 (66.7)	17 (63.0)	15 (71.4)	0.758[p]
	> 38	16 (33.3)	10 (37.0)	6 (28.6)	

[u] — Mann Whitney U test (Monte Carlo), [p] — Pearson Chi-Square Test (Exact), [f] — Fisher Exact test (Exact), Med — Median, Min — Minimum, Max — Maximum

AFI < 5 cm vs AFI > 5 cm groups, whereas a higher frequency of 1-min Apgar scores < 7, neonatal sepsis and early neonatal mortality in AFI < 3 cm vs AFI > 3 cm groups [8].

Association of AFI scores < 5 cm with increased risk of chorioamnionitis and early onset neonatal sepsis [20, 21] as well as an association of AFI scores with APGAR scores, neonatal respiratory distress syndrome and maternal chorioamnionitis [15] were also reported in other studies.

Besides, although oligohydramnios has been suggested as an important parameter in the evaluation of fetal wellbeing and a warning sign for predicting poor fetal prognosis in pregnancies complicated by PPROM [8, 12, 14, 15, 18, 19], there is no consensus on the optimal time to induce labor to enable a reduction of perinatal risks [7, 8].

Indeed, comparable to findings in our cohort, lack of association between AFI scores and adverse outcomes in pregnancies complicated by PPROM was also reported in other studies [5, 15]. In a past study of 161 singleton pregnancies complicated by PPROM, authors reported that AFI < 5 cm and AFI ≥ 5 cm were similar in terms of gestational age at rupture of the membranes, gestational age at the delivery, mode of delivery, maternal chorioamnionitis, abruption, early onset neonatal sepsis and NICU stay as well as fetal birth weight [5]. No significant association of AFI with APGAR scores, neonatal RDS and maternal chorioamnionitis was also reported in another study [15].

Notably, in a retrospective cohort study in 92 women with PPROM, authors reported association of persistent

Table 3. Fetal complications with respect to AFI

		Total (n = 48)	AFI < 5 cm (n = 27)	AFI ≥ 5 cm (n = 21)	P
Number of complications, Median (Min/Max)		2 (0/5)	2 (0/5)	2 (0/5)	0.563[u]
		n (%)	n (%)	n (%)	
Complications					
	Absent	13 (27.1)	6 (22.2)	7 (33.3)	0.516[p]
	Present	35 (72.9)	21 (77.8)	14 (66.7)	
ICU stay					
	Absent	16 (33.3)	8 (29.6)	8 (38.1)	0.758[p]
	Present	32 (66.7)	19 (70.4)	13 (61.9)	
Sepsis					
	Absent	40 (83.3)	22 (81.5)	18 (85.7)	0.999[f]
	Present	8 (16.7)	5 (18.5)	3 (14.3)	
Meconium aspiration					
	Absent	46 (95.8)	26 (96.3)	20 (95.2)	–
	Present	2 (4.2)	1 (3.7)	1 (4.8)	
Respiratory distress syndrome					
	Absent	23 (47.9)	12 (44.4)	11 (52.4)	0.771[p]
	Present	25 (52.1)	15 (55.6)	10 (47.6)	
Intraventricular hemorrhage (Grade 3–4)					
	Absent	47 (97.9)	26 (96.3)	21 (100.0)	–
	Present	1 (2.1)	1 (3.7)	0 (0.0)	
Umbilical artery pH					
	< 7.1	43 (89.6)	24 (88.9)	19 (90.5)	0.999[f]
	> 7.1	5 (10.4)	3 (11.1)	2 (9.5)	
5th min Apgar score					
	< 5	25 (52.1)	14 (51.9)	11 (52.4)	0.999[p]
	> 5	23 (47.9)	13 (48.1)	10 (47.6)	

[u] — Mann Whitney U test (Monte Carlo), [p] — Pearson Chi–Square Test (Exact), [f] — Fisher Exact test (Exact), Med — Median, Min — Minimum, Max — Maximum

Table 4. Correlation of AFI with other study parameters

	AFI	
	r	P
Age	0.043	0.771
Gravidity	–0.118	0.425
BMI	–0.162	0.270
PPROM time	–0.120	0.417
Delivery week	0.044	0.765
Birth weight	0.146	0.321
Latency period (day)	0.339	**0.018**
Post–partum length of hospital stay (day)	–0.314	**0.030**
Total number of maternal complications	–0.192	0.191
Total number of fetal complications	–0.0002	0.999

Spearman's rho test, r — Correlation Coefficient

oligohydramnios with lower postnatal survival rate and more frequent developmental delay among neonates as compared with normal amniotic fluid volume, whereas they also indicated that most neonates born alive after PROM and persistent oligohydramnios to survive to discharge and to be developmentally normal [22]. Similarly, while prolonged oligohydramnios following PPROM has traditionally been associated with poor fetal outcomes including high neonatal mortality, an apparent improvement in outcome has also been emphasized recently even amongst the highest risk infants with documented persistent oligohydramnios [16].

Hence, the controversy regarding the association of oligohydramnios with adverse maternal and neonatal outcome in PPROM in published studies seems to emphasize the need for this association to be investigated by further larger scale studies with sufficient number of patients with low AFI [5, 12, 20, 23].

Although, higher fetal birth weight in the AFI ≥ 5 cm group as compared with AFI < 5 cm group in our cohort seems consistent with previously reported role of AFI in predicting macrosomia in a prospective observational study

in 600 patients in the first stage of labor before rupture of membranes [24], it should be noted that latency period and the mean gestational age at the delivery also differed between AFI groups emphasizing the birthweight to be variable dependent on gestational age and placental factors rather than on residual AFI.

In fact, while oligohydramnios has been associated with a higher likelihood of caesarean section due to non–reassuring fetal heart rate patterns [5, 12, 20] as well as with longer NICU stay [25], our findings revealed similar cesarean section delivery rates and length of NICU stay in AFI ≥ 5 cm and < 5 cm groups. Nevertheless, caesarean section rate (18.8%) in our cohort of women with pregnancies complicated by PPROM at 23–33 weeks' gestation seems in accordance with the likelihood of an increased risk of maternal infection in cesarean sections, particularly in women at risk of developing chorioamnionitis [23, 26].

CONCLUSIONS

In conclusion, our findings seem to indicate increased likelihood of shorter latency to delivery and longer postpartum LOS with decrease in AFI after PPROM between 23–33 weeks' gestation, whereas no impact of AFI on mode of delivery and fetal or maternal complications. Further larger scale longitudinal studies in pregnant women with PPROM are needed to investigate the utility of AFI as a potential prognostic variable in predicting adverse fetal or maternal outcomes.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Informed consent

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study.

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