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Urea and Creatinine Levels in Vaginal Fluid as A Predicator for Length of Latency Period in Prelabour Membranes Rupture

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ABSTRACT

Background: The diagnosis of equivocal cases of prelabour rupture of membranes (PROM) with traditional methods has been unreliable therefore various biochemical markers have been sought to confirm the same, this study aims to determine the relation between the concentration of urea and creatinine in vaginal fluid and length of latency period in women with PROM between 32 and 35 weeks gestation.

Methods: sixty patients were included in our study with PROM of their singleton pregnancies, their gestational age ranged between 32- 35 gestational weeks by reliable menstrual history and confirmed by pelvi-abdominal ultrasound. All samples were obtained within 6 hours after membranes rupture before vaginal examination and the administration of any drugs All women will be put under observation for 48 hours and time of onset of delivery will be documented, the onset of labor will be diagnosed by either: frequent uterine contractions more than 2 contractions in 10 minutes or CTG showing frequent contractions.

Results: The current study was conducted on a total number of 60 pregnant women, 20-35 year old; pregnant between 32 and 35weeks. Our study demonstrated that patients with higher levels of vaginal fluid urea and creatinine concentrations had earlier onset of labor. Patients with vaginal fluid urea and creatinine concentrations above cut-off levels (urea ≥26.0 (mg/dL), creatinine ≥0.64 (mg/dL)) went into labor early within a 48 hours latency period. This suggests vaginal urea and creatinine levels measurement in the prediction of early delivery.

Conclusion: Measurement of urea and creatinine in vaginal fluid is a cheap and rapid method with high sensitivity and specificity for the delivery interval after PROM. Therefore, these methods can be integrated as non-invasive tests for the predication of delivery interval after PROM.

Keywords: Prelabour rupture of membranes (PROM); Amniotic fluid (AF); Amniotic fluid index (AFI); Respiratory distress syndrome (RDS)

INTRODUCTION

Prelabour rupture of the membranes (PROM) constitutes one of the most important dilemmas in current obstetric practice; it could be defined as rupture of the fetal membranes preceding the onset of labor [1].

The optimal management of pregnancies complicated by PROM remains an area of great controversy in obstetrics [2].

One issue of paramount importance is the decision to initiate expectant management versus immediate delivery. Expectant management allows for prolongation of pregnancy with the potential for improvement in neonatal outcome. However, expectant management does pose significant maternal and neonatal risks [3]; in addition to potential risks such as chorioamnionitis, cord prolapse and placental abruption[4]. In a randomized controlled trial in 2012, David van der Ham and colleagues, investigated induction of labor versus expectant management for women with prelabour rupture of membranes and their primary outcome was the rate of neonatal sepsis (the proportion of babies that develop neonatal sepsis) and secondary outcomes were the rates of neonatal respiratory distress syndrome (RDS), cesarean section (surgical delivery), and chorioamnionitis in women with PROM between 34 and 37 weeks' gestation. All of which may support an active management approach to women with PROM. However, 70% of women with term PROM who were managed expectantly were reported to deliver within 24 hours, while only 15% were not delivered up to 48 hours[5].

Among women with suspected prelabour rupture of the membranes (PROM), an important question in clinical practice is whether or not the woman will soon be in spontaneous labor, therefore the ability to predict the latency period

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of women with term PROM may aid to optimize the management of such women [6].

Numerous studies have previously reported regarding factors predicting prolonged latency period in women presenting with PROM [7], some of the suggested factors were gestational age at admission [8], amniotic fluid index (AFI) and parity [9].

Urea plays an important role in the metabolism of nitrogen-containing compounds in the urine [10].Creatinine is a break-down product of creatinine phosphate in muscles and is usually produced at a fairly constant rate and is mainly filtered out of the blood by kidneys [11].

The fetal kidneys start to develop during the 4th and 5th weeks of gestation and begin to excrete urine into the amniotic fluid at the 8th to 11th week. At the 20th week, the fetal kidneys produce most of the amniotic fluid; therefore, important changes are expected in the composition of amniotic fluid as gestation progresses [12].

Kafali and Oksuzler [13] hypothesized that vaginal fluid urea and creatinine might be useful in diagnosis of PROM in light of the fact that fetal urine is the most essential source of amniotic fluid in second half of pregnancy.

Creatinine concentration in amniotic fluid increases gradually between 20 to 32 weeks of gestation and more rapidly thereafter, when it is two to four times higher than in maternal serum [13]. Oliveira et al. [12] have found that creatinine concentration of 1.75 mg/dl or more correlates fundamentally with a gestational age of 37 weeks or more.

Mean vaginal fluid urea and creatinine concentrations in women who delivered within 48 hours were significantly higher compared to women who delivered after 48 hours. Among those women with urea concentrations of > 19.4 mg/dl, the median time between PROM and delivery was significantly lower when compared to those with urea concentrations of < 19.4mg/dl women with creatinine levels of > 0.23 mg/dl had significantly lower delivery intervals compared to those with creatinine levels of < 0.23 mg/dl [15].

Aim of the work: a prospective observational including the relation between the concentration of urea and creatinine in vaginal fluid and length of latency period in women with PROM between 32 and 35 weeks gestation.

PATIENTS AND METHODS

Study population

Sixty pregnant women with PPROM with singleton pregnancies with a gestational age between 32- 35 gestational weeks by reliable menstrual history and confirmed by pelvi-abdominal ultrasound.

Membrane rupture was diagnosed by the direct visualization of fluid leakage from the cervical canal using sterile speculum.

Inclusion criteria

1- Maternal age between 20-35 years.
2- 32-35 weeks gestational age.
3- Viable fetus.

Exclusion criteria

1. Vaginal bleeding either spontaneous or traumatic e.g. placenta previa.
2. Chorioamnionitis.
3. Multiple pregnancies.
4. Presence of uterine contractions.
5. Amniotic fluid disorders e.g. polyhydraminos
6. Meconium stained amniotic fluid prior to active phase of labor.
7. Maternal disease necessitating termination of pregnancy e.g. severe preeclampsia

Sample size justification

The required sample size has been calculated using the Power Analysis and Sample Size (PASS©) software version 11.0.10 (NCSS©, LLC, Kaysville, Utah).

The primary outcome measure is the accuracy of vaginal fluid urea or creatinine for prediction of delivery within 48 hours in patients with PROM.

A previous study reported that 41.7% of women with PROM delivered within 48 hours from PROM, vaginal fluid urea had a sensitivity of 85.7% and specificity of 85.7%, while creatinine had a sensitivity of 88.5% and specificity of 83.7% [15].

These calculations used a two-sided binomial test with a confidence level of 99% (type I error, 0.01) and assumed that the incidence of delivery within 48 hours from PROM is 41.7% [15].

Procedure

- Patients were subjected to full history taking and general examination.
- Local examination was done as follows:

All women were put in dorsal lithotomy position, using a proper light source and sterile gloves; sterile speculum free of gel will be placed into vagina.

For every woman a specimen of vaginal fluid were taken as follows: 5 ml of sterile saline solution will be injected into the posterior vaginal fornix taken after aspiration of 3ml with the same syringe.

All samples had been obtained within 6 hours after membranes rupture before vaginal examination and the administration of any drugs. Upon collection, samples were centrifuged at 3000 rpm for 10 minutes and supernatant fluid was separated. Exact concentrations of urea and creatinine will be measured immediately. All women had been under observation for 48 hours and time of onset of delivery was documented, the onset of labor had been diagnosed by either frequent uterine contractions more than 2 contractions in 10 minutes or CTG showing frequent contractions.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical analysis

Sensitivity, specificity, positive predictive value, and negative predictive value were also calculated. Data will be collected, tabulated, then analyzed using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY). Normally distributed numerical data will be presented as mean and SD, and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage. Comparison of normally distributed numerical data will be done using the unpaired student t test. Skewed data will be compared using Mann-Whitney U test. Categorical data will be compared using Chi-squared test, or Fisher's exact test when appropriate. Receiver-operating characteristic (ROC) curve analysis will be used to examine the predictive value of vaginal fluid urea or creatinine. A two-sided p-value <0.05 will be considered statistically significant.

RESULTS

Table (1): Comparison between cases who had latency period less and more than48 hours

Variable	≤ 48 hours (N=26)	> 48 hours (N=34)	P
Age (years)	29.2±3.6	29.5±4.1	0.768
BMI (Kg/m^2)	28.5±2.2	28.5±2.1	0.934
Parity	2.2±0.9	1.2±1.1	**<0.001***
GA (weeks)	34.0±0.4	33.3±0.6	**<0.001***
Urea (mg/dL)	30.5±3.7	24.9±3.2	**<0.001***
Creatinine (mg/dL)	0.69±0.16	0.51±0.14	**<0.001***

^Independent t-test, *Significant

Table (1) showing that Cases with latency period less than or equal 48 hours had significantly higher **parity, GA, urea and creatinine.**

Table (2): Linear regression model for factors predicting Latency period

Factors	B	SE	P	95% CI	R^2
Constant	118.316	7.809	**<0.001***	102.679–133.954	0.633
Parity	-2.586	1.202	**0.036***	-4.992–-0.180	
Urea (mg/dL)	-2.397	0.306	**<0.001***	-3.009–-1.785	

β: Regression coefficient, SE: Standard error, CI: Confidence interval, R^2: Coefficient of determination

Linear logistic analysis done for factors affecting **Latency period** revealed that, only **constant, parity and urea** were significant predictors. The predicting equation explained 63.3% of the variability of latency period of cases with the studied inclusion and inclusion criteria.

Latency period (hours) = 118.316 - 2.586*parity - 2.397*urea (mg/dL)

Table (3): Diagnostic performance of variables in predicting latency period within 48 hours

Factors	AUC	SE	P	95% CI	Cut off
GA	0.785	0.059	**<0.001***	0.668–0.901	--
Parity	0.734	0.066	**0.002***	0.606–0.863	--
Urea	0.879	0.047	**<0.001***	0.787–0.970	≥26.0
Creatinine	0.827	0.056	**<0.001***	0.716–0.937	≥0.64
Equation	0.882	0.044	**<0.001***	0.795–0.969	≥48.0

AUC: Area under curve, SE: Standard error, CI: Confidence interval, *significant

Table (3) and figure (1) show that: **GA and parity** had significant low diagnostic performance in predicting latency period within 48 hours. **Urea, creatinine and predicting equation** had significant moderate diagnostic performance in predicting latency period within 48.

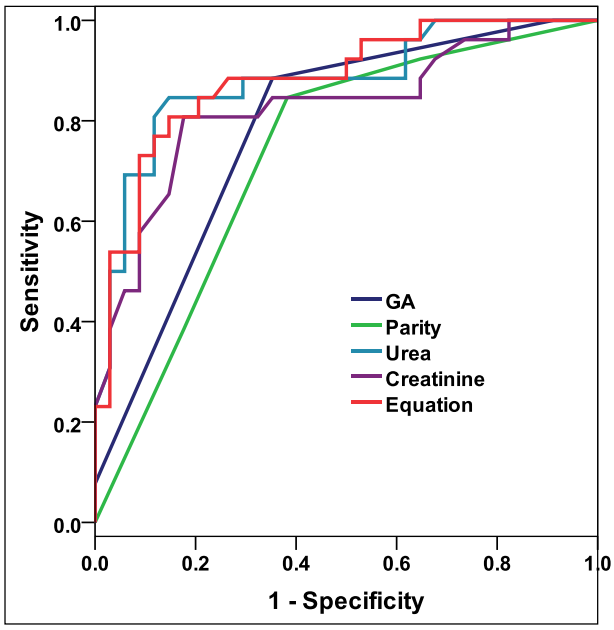

Figure (1): ROC curve for the studied variables in predicting latency period within 48 hours

Table (4): Diagnostic characteristics of urea≥26.0 (mg/dL) in prediction of latency period within 48 hours

Characters	Value	95% CI
Sensitivity	84.6%	65.1%–95.6%
Specificity	82.4%	65.5%–93.2%
Diagnostic accuracy (DA)	83.3%	71.5%–91.7%
Youden's index	67.0%	48.1%–85.9%
Positive Predictive value (PPV)	78.6%	59.0%–91.7%
Negative Predictive value (NPV)	87.5%	71.0%–96.5%
Positive likelihood ratio (LR+)	4.79	2.28–10.09
Negative likelihood ratio (LR-)	5.35	2.14–13.36
Diagnostic odd ratio (LR)	25.67	6.44–102.32
Kappa coefficient	0.66	0.47–0.85

CI: Confidence interval

Vaginal fluid urea ≥26.0 (mg/dL) had moderate diagnostic characteristics in prediction of latency period within48 hours.

Table (5): Diagnostic characteristics of creatinine≥0.64 (mg/dL) in prediction of latency period within 48 hours

Characters	Value	95% CI
Sensitivity	80.8%	60.6%–93.4%
Specificity	82.4%	65.5%–93.2%
Diagnostic accuracy (DA)	81.7%	69.6%–90.5%
Youden's index	63.1%	43.3%–83.0%
Positive Predictive value (PPV)	77.8%	57.7%–91.4%
Negative Predictive value (NPV)	84.8%	68.1%–94.9%
Positive likelihood ratio (LR+)	4.58	2.16–9.69
Negative likelihood ratio (LR-)	4.28	1.92–9.56
Diagnostic odd ratio (LR)	19.60	5.26–72.99
Kappa coefficient	0.63	0.43–0.83

CI: Confidence interval

Vaginal fluid creatinine ≥0.64 (mg/dL) had moderate diagnostic characteristics in prediction of latency period within48 hours.

Table (6): Diagnostic characteristics of predicted equation≥48.0 (hours) in prediction of latency period within 48 hours

Characters	Value	95% CI
Sensitivity	80.8%	60.6%–93.4%
Specificity	82.4%	65.5%–93.2%
Diagnostic accuracy (DA)	81.7%	69.6%–90.5%
Youden's index	63.1%	43.3%–83.0%
Positive Predictive value (PPV)	77.8%	57.7%–91.4%
Negative Predictive value (NPV)	84.8%	68.1%–94.9%
Positive likelihood ratio (LR+)	4.58	2.16–9.69
Negative likelihood ratio (LR-)	4.28	1.92–9.56
Diagnostic odd ratio (LR)	19.60	5.26–72.99
Kappa coefficient	0.63	0.43–0.83

CI: Confidence interval

Predicted equation ≥ 48.0 (hours) had moderate diagnostic characteristics in prediction of latency period within48 hours.

From the above date we found that, there were significant negative correlations between latency period and urea& creatinine. Urea and parity could be combined in a predicting equation for latency period. Vaginal fluid urea ≥ 26.0 (mg/dL) & creatinine ≥ 0.64 (mg/dL) had moderate diagnostic characteristics in prediction of labour within 48 hours.

DISCUSSION

The current study was conducted on a total number of 60 pregnant women (20-35) year old; pregnant between 32 and 35 weeks.

We found that vaginal urea and creatinine levels in patients who underwent delivery within 48 hours were significantly higher than those in patients who were delivered after 48 hours.

Previous studies have observed that both urea and creatinine levels in amniotic fluid were significantly increased throughout gestation [12]. This increase was found to be gradual between 20 and 32 weeks of gestation and more rapidly thereafter [16]; it seems evident that the origin of these two markers is a function of filtration in the fetal kidneys maturation of tubular function.

This relatively high rate of women with prolonged latency period necessitated the search for predictors of prolonged latency, in order for better counseling women with PROM and to manage early delivery.

Numerous studies have previously reported regarding factors predicting prolonged latency period in women presenting with PROM, Some of the suggested factors were gestational age at admission [8], amniotic fluid index (AFI), and parity [9].

Our study demonstrated that patients with higher levels of vaginal fluid urea and creatinine concentrations had earlier onset of labor and that there were significant negative correlations between latency period and parity, GA, urea & creatinine. Patients with vaginal fluid urea and creatinine concentrations above cut-off levels went into labor early That was demonstrated in Table (4) where Vaginal fluid urea≥26.0 (mg/dL) had moderate diagnostic characteristics in prediction of latency period within 48 hours, while Table (5) was showing Vaginal fluid creatinine ≥0.64 (mg/dL) had moderate diagnostic characteristics in prediction of latency period within 48 hours. This suggests a role of vaginal urea and creatinine levels in the prediction of early delivery.

In accordance with our study only Gezer et al. [15] has reported vaginal fluid creatinine level> 0.23mg/dL as a predictor of latency period within 48 hours while urea level > 19.4mg/dL as a predictor of latency period within 48 hours.

The difference between our cut-off levels and Gezer et al.cut-off levels[15]return to the use of wide range of gestational age in Gezer et al. [15] study between 24 till 34 gestational weeks while our study between 32-35 gestational weeks.

Linear logistic analysis done for factors affecting Latency period revealed that, only constant, parity and urea were significant predictors. The predicting equation explained 63.3% of the variability of latency period of cases with the studied inclusion and inclusion criteria. Table (3) and figure (1) show that: GA and parity had significant low diagnostic performance in predicting latency period within 48 hours. Urea, creatinine and predicting equation had significant diagnostic performance in predicting latency period within 48 showing urea sensitivity 84.6%, specificity 82.4%, positive predictive value 78.6% and negative predictive value 87.5% while for creatinine sensitivity 80.8%, specificity 82.4% positive predictive value 77.8% and negative predictive value 84.8% and predicting equation sensitivity 80.8%, specificity 82.4% positive predictive value 77.8% and negative predictive value 84.8%

A possible explanation for the lack of significance of other factors such as gestational age for the prediction of prolonged latency at term can be related to the relatively short interval that was used to differentiate those with short and prolonged latency periods.

Latency period (hours) =18.316 - 2.586*parity - 2.397*urea (mg/dL)

From the above date we find that, there were significant negative correlations between latency period and urea& creatinine. Urea and parity could be combined in a predicting equation for latency period. Vaginal fluid urea≥26.0 (mg/dL) & creatinine ≥0.64 (mg/dL) had moderate diagnostic characteristics in prediction of labour within 48 hours.

The strengths of our study include a relatively large sample size, prospective nature of study design while the main limitation of the study is that false positive diagnosis may occur in cases where visual inspection is uncertain.

CONCLUSION

Measurement of urea and creatinine in vaginal fluid is a cheap and rapid method with high sensitivity and specificity for the delivery interval after PROM. Therefore, these methods can be integrated as non-invasive tests for the predication of delivery interval after PROM.

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