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Quantitative vaginal fluid creatinine in prelabor rupture of membranes (PROM): factors associated with diagnostic power

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Abstract

Introduction: Prelabor rupture of membranes (PROM) remains a challenge in obstetrics with serious complications. Quantitative vaginal fluid creatinine concentration is a promising test for diagnosing PROM in resource-limiting settings. However, uncovered factors may affect the diagnostic power of this potential test. We aimed to investigate how clinical factors may affect this diagnostic power.

Methods: We conducted a case-control diagnostic test study at Hung Vuong Maternity Hospital, Vietnam. Pregnant women between 24–42 weeks were enrolled into case and control groups, with a ratio of 1:2. Sterile speculum examination for fluid leak from cervix, nitrazine test and ferning test were used to determine membranes' status. Quantitative creatinine from vaginal fluid was measured using the Jaffe method. We calculated sensitivity and specificity to describe the test's diagnostic power. The receiver operating characteristic (ROC) curve and Youden's J statistic were used to identify the optimal cut-off value of the test. Logistics regression models were used to detect factors that may affect the diagnostic power of the test. Ethics approval was obtained from the local ethics committee and all participants gave written informed consent.

Results: We recruited a total of 693 pregnant women into the study – 231 participants in the study group and 462 participnts in the control group. There were two clinical factors affecting diagnostic power of quantitative vaginal fluid creatinine concentration: dilated cervix [OR=6.08(4.26–8.68); p<0.001) and urinary incontinence [OR=0.52(0.29–0.92); p=0.03). The optimal cut-off value for creatinine concentration is 0.29 mg/dL in the general group, in the closed cervix group and in the group with no urinary incontinence during pregnancy. The dilated cervix group provided a lower cut-off value (0.26 mg/dL) while the urinary incontinence group had a higher cut-off value (0.31 mg/dL). They both had lower diagnostic powers compared to the general group. However, the test accuracy, sensitivity and specificity remain above 90% in all subgroups.

Conclusions: Quantitative creatinine in vaginal fluid is a potential diagnostic test for PROM in resource-limiting settings. Doctors should remain vigilant about its limitation in clinical applications.

Keywords: prelabor rupture of membranes (PROM); creatinine; urinary incontinence; dilated cervix

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1. INTRODUCTION

Prelabor rupture of membranes (PROM) is a common challenge in managing pregnancy, which happens in 10% of normal pregnancies and nearly 4% of preterm pregnancies. The conditions can complicate the delivery process, increasing the risk of preterm birth as well as infection for both mother and child [1],[2]. PROM remains a challenging issue in obstetrics as nearly 30% of cases are either over-diagnosed or under-diagnosed [3]. Over-diagnosed cases can lead to over-interventions, including prolonged hospitalization, misuse of antibiotics, and inappropriate termination of pregnancy. Under-diagnosed cases delay life-saving interventions such as antibiotics, hospital administration, steroids, or termination of pregnancy. All of these can significantly increase the morbidity and mortality of both the mother and the child. Therefore, it is vital to identify PROMs accurately and in a timely manner.

Diagnosing PROMs can be a challenge in clinical practice. Non-invasive criteria that are considered the gold standard include (1) amniotic fluid leaking from the cervix or pooling in the posterior vaginal wall via speculum examination, (2) a positive Nitrazine test and, (3) a positive ferning test. A definitive diagnosis requires all three criteria. However, it is not uncommon to see cases that do not meet all these criteria, and this is a challenge in clinical practice. Many researchers have proposed different solutions for this issue, including the injection of colored chemical compounds into the amniotic fluid and detecting its leakage in vaginal fluid. However, this invasive method carries significant risks of devastating complications for both mother and fetus. This is why this method is no longer used in clinical practice [4] and the quest to find the ideal test remains.

In recent years, there have been several novel tests to diagnose PROM. The principle of these tests is detecting specific compounds that are only present in the amniotic fluid or have a significantly higher concentration in amniotic fluid compared to vaginal fluid. These markers include fetal fibronectin, alpha-fetoprotein, insulin growth factor binding protein-1, human chorionic gonadotropin, and prolactin [5]–[7]. The FDA recently approved a rapid diagnostic test for ruptured membranes – PMAG-1 (AmniSure), which provides high sensitivity and specificity. However, the expensive price of these tests is a major factor that prevents them from having clinical impacts in LMIC settings. Affordable and high diagnostic capabilities are important factors for clinical application in resource-limited settings.

Recent studies have identified vaginal fluid creatinine level as a potential candidate test for identifying PROM [8]. This relies on the hypothesis that most amniotic fluid is the fetus's urine produced in the second and third trimesters. Signature compounds for urine such as creatinine will have a significantly higher concentration in the amniotic fluid than in the vaginal fluid. Therefore, high levels of creatinine in the vaginal fluid could serve as an indicator of ruptured membranes. Many studies conducted in LMICs have suggested that creatinine concentration in vaginal fluid could be a useful test, with high sensitivity and specificity [9]–[11]. However, the cutoff values for diagnosing ruptured membranes are inconsistent between studies, and researchers have suggested certain factors that could affect the creatinine concentration in vaginal fluid. It is crucial to identify these potential confounding variables and the clinicians should remain vigilant about the limitation of the tests in case these factors are present. Therefore, we conducted the study to investigate the effect of factors associated with creatinine levels in vaginal fluid.

2. METHODS

2.1. Study settings

The study was designed as a prospective study on diagnostic test for PROM, conducted at Hung Vuong Maternity Hospital, Ho Chi Minh City, Vietnam. Recruitment was conducted from the 15th of June 2021 to the 1st of March 2022.

2.2. Study design and participants

2.2.1. Study design

This was a case-control diagnostic test study. Pregnant women were enrolled into two groups: the group with confirmed membranes ruptured (case group) and the group with

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the membranes intact (control group). The ratio between the case group to control group is 1:2.

2.2.2. Study participants

All pregnant women at the gestational age between 24–42 weeks who visited Hung Vuong Maternity Hospital emergency room and antenatal clinic were eligible for screening. The gestational age was confirmed by either the last menstrual cycle method or ultrasound in the first trimester, recorded in the patient's medical record. The exclusion criteria included: patient younger than age 18, patient could not provide informed consent, recent vaginal bleeding in pregnancy, and stillbirth or fetal renal abnormalities. In the case group, the inclusion criteria included pregnant women who went to the emergency room for suspected membrane rupture without ongoing active uterus contractions. In the control group, women who visited the hospital for routine antenatal checkups and had no signs of suspected membrane rupture were eligible for screening.

2.2.3. Data collection and tools

We used the following three criteria to confirm the membranes' status: a sterile speculum examination to observe fluid leakage from the cervix or free fluid in the posterior fornix, the nitrazine test, and the ferning test. A sterile speculum examination was performed by one of the study team clinicians, checking for any fluid flowing from the cervix and if there was any free fluid present in the posterior fornix. After this, the nitrazine test and the ferning test were carried out. If the nitrazine paper turned blue, it was considered a positive result and vaginal washing fluid was collected to determine the concentration of creatinine. To do this, firstly, the clinician injects five mL of sterile saline into the posterior vaginal fornix, waits 30 seconds and then uses the same syringe to withdraw three mL of fluid. The sample is then sent to the hospital laboratory for a quantitative creatinine test by using the Jaffe chemical calorimetric method.

Convenience sampling was used in the case group. Confirmed PROM was defined as having met all three criteria mentioned above, which are a positive fluid leakage from the cervix or free fluid in the posterior fornix during sterile speculum examination, a positive nitrazine test, and a positive ferning test. All participants in the emergency room who were confirmed diagnosed with PROM were included in the analysis. Pregnant women who came to the antenatal clinic with matched gestational age to one of the participants in the case group, and met all three negative criteria: no fluid leakage from the cervix or free fluid in the posterior fornix during sterile speculum examination, a negative nitrazine test and a negative ferning test were also included in the analysis. Participants who did not meet these criteria for either group were excluded from the analysis and their collected samples were disposed of according to hospital policy.

All participants were consulted and examined by a clinician on the study team. A detailed patient history, including both comorbidity and previous pregnancy, was collected in a defined form. Demographic and obstetric characteristics, signs of suspected membrane ruptures, general and abdominal examinations, and test results were collected as routine hospital procedures. This information was written in the paper case report form. After completing the study procedures, patients continued their treatment following the hospital standard protocols.

2.3. Sample size and sampling

Sample size calculation was based on the estimation of the area under the curve (AUC) in the diagnosis of PROM by creatinine concentration in vaginal fluid. From a previous study [10] we chose the AUC=0.902, with α=0.05, estimation error=0.035, and the ratio between case to control being 1:2. Based on these values, the calculated sample size was 215 for the case group and 430 for the control group.

2.4. Statistical method

Data entry was performed using Microsoft Excel 2013 (Microsoft®). The principal investigator checked and validated the data after the first data entry. Data curation and analysis were conducted using RStudio version 1.4.1103 (RStudio, PBC). Data were presented as count and percentage for each group and odds ratio (OR) was used to describe the association between groups. We used logistic regression models to detect any confounding factors. We considered a

variable as confounding when the p-value of this variable with creatinine concentration was lower than 0.05. Stepwise logistic regression models were used to classify membrane status. The model with the lowest Akaike Information Criteria (AIC) value was chosen as the optimal model. Subgroup analysis was performed to investigate the diagnostic power of quantitative creatinine in each circumstance. Sensitivity, specificity, and accuracy were used to evaluate the diagnostic power. The receiver operating characteristic (ROC) curve and Youden's J statistic were used in combination to choose the optimal cut-off point for creatinine concentration in vaginal fluid.

2.5. Ethical considerations

The study protocol was reviewed and approved by the Hung Vuong Maternity Hospital Ethics Committee (reference number 1868/HĐĐĐ-BVHV). All pregnant women who participated in the study were consulted and each provided their written informed consent.

3. RESULTS

From June 2021 to March 2022, a total of 725 pregnant women were screened for the study and 693 women were recruited as participants into the study. In the case group, we screened 248 pregnant women, of which five women had at least one exclusion criterion and 12 women did not have all three criteria to confirm PROM. In the control group, we screened 477 pregnant women, of which 11 women had at least one exclusion criterion and four women had at least one criterion for diagnosing ruptured membranes. In summary, 231 participants were recruited into the case group and 462 participants into the control group. This satisfied the planned sample size, and all 693 participants' data was included in the final analysis. Table 1 describes the characteristics of previous pregnancy and illness, stratified by study group.

Considering the patients' histories, there were no significant differences between the two groups in comorbidity, incompetent cervix, previous pregnancy (full term, preterm, abortions, and living children), placenta previa, and fetal abnormalities (IUGR, fetal congenital anomalies). All of these had a p-value higher than 0.05.

Full-term pregnancy and a history of diabetes were significantly different between the two groups. The OR in patients with diabetes was reduced by nearly half compared to non-diabetic patients ($p<0.001$). The OR (of ruptured membranes) in patients with one full-term birth was reduced by 31%, and in patients with two full-term births was reduced by 43% ($p<0.05$).

We also looked at the characteristics of current pregnancies for potential factors associated with ruptured membranes. These are presented in Table 2.

Urinary incontinence during pregnancy, uterus contraction and cervix opening status were significantly different between the case and control groups. In patients with uterus contraction, the OR of ruptured membranes was 1.66 times that of patients without uterus contraction ($p=0.002$). In patients with 1–2 cm dilated cervix, the OR of ruptured membranes was multiplied by 6.06 compared to patients with closed cervix ($p=0.001$). The OR of ruptured membranes in urinary incontinence patients were only 0.52 times that of non-urinary-incontinence patients ($p=0.03$). There were no significant differences between the two groups when considering the type of urinary incontinence and the gestational-age group.

From the result of univariate logistic regression shown in Table 2, we identified three factors that might affect the creatinine level of vaginal fluid. These were urinary incontinence, uterus contraction, and cervix status (whether it was dilated or closed). From the clinical point of view, we added the following variables of the mother's age, diabetes history, gestational age, history of term pregnancy, and fetus IUGR into the initial multivariate logistic regression model. These clinical variables were added because they are well-known important clinical features that generally affect the outcome of the pregnancy. The result of this model was shown in Table 3.

We aimed to achieve an optimal model that could balance the diagnostic power and the least number of variables needed. Therefore, stepwise logistic regression was used to identify the optimal model to classify the membrane status. The model, which included urinary incontinence, cervix status, and Log (Creatinine +0.1), provided the lowest AIC

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Table 1. Characteristics of previous pregnancy by study group

Characteristics	Case group (n=231)	Control group (n=462)	OR (95% CI)	p[1)]
Incompetent cervix (n=369)				
No	107 (99.1)	261 (100)	1	
Yes	1 (0.9)	0 (0.00)	7.29 (0.29–180.56)	0.29
Comorbidity				
No	210 (90.9)	429 (92.9)	1	
Cardiovascular	2 (0.9)	3 (0.7)	1.39 (0.16–9.22)	0.73
Endocrinology	3 (1.30)	4 (0.8)	1.55 (0.28–7.47)	0.58
Hematology	6 (2.60)	9 (1.9)	1.37 (0.45–3.92)	0.56
Others	10 (4.3)	17 (3.7)	1.21 (0.52–2.66)	0.64
Term pregnancy				
0	130 (56.3)	211 (45.7)	1	
1	76 (32.9)	180 (39.0)	0.69 (0.48–0.97)	0.03
≥2	25 (10.8)	71 (15.4)	0.57 (0.34–0.95)	0.02
Preterm pregnancy				
0	221 (95.7)	449 (97.2)	1	
≥1	10 (4.33)	13 (2.81)	1.57 (0.65–3.65)	0.31
Abortions				
0	181 (78.4)	362 (78.4)	1	
1	39 (16.9)	76 (16.5)	1.03 (0.67–1.57)	0.89
≥2	11 (4.76)	24 (5.19)	0.92 (0.42–1.89)	0.83
Living children				
0	124 (53.7)	206 (44.6)	1	
1	80 (34.6)	184 (39.8)	0.72 (0.51–1.02)	0.06
≥2	27 (11.7)	72 (15.6)	0.63 (0.38–1.02)	0.06
Diabetes				
No	197 (85.3)	345 (74.7)	1	
Yes	34 (14.7)	117 (25.3)	0.51 (0.33–0.77)	0.001
Pre–eclampsia				
No	224 (97.0)	454 (98.3)	1	
Yes	7 (3.03)	8 (1.73)	1.78 (0.60–5.10)	0.287
IUGR				
No	224 (97.0)	437 (94.6)	1	
Yes	7 (3.0)	25 (5.4)	0.55 (0.23–1.28)	0.16
Placenta previa				
No	231 (100)	461 (99.8)	1	
Yes	0 (0.00)	1 (0.2)	0.66 (0.03–16.37)	0.80
Fetal congenital anomalies				
No	230 (99.6)	459 (99.4)		
Yes	1 (0.4)	3 (0.6)	0.72 (0.03–6.28)	0.78

[1)] Univariate logistic regression.
OR, odds ratio.

(AIC=183) and thus was chosen as the optimal model. This final model left out the following variables: mother's age, diabetes history, gestational age, history of term pregnancy, fetus IUGR, and uterus contractions.

After identifying that cervix status and urinary incontinence may affect the diagnostic power of the test, we per-

Table 2. Characteristics of current pregnancy by study group

Characteristics	Case group (n=231)	Control group (n=462)	OR (95% CI)	p[1)]
Gestational age (weeks)				
24–34	27 (11.7)	54 (11.7)	1	
34–41	204 (88.3)	408 (88.3)	1.00 (0.60–1.63)	0.99
Urinary incontinence				
No	215 (93.1)	404 (87.4)	1	
Yes	16 (6.93)	58 (12.6)	0.52 (0.29–0.92)	0.03
Type of urinary incontinence (n=74)				
Stress (pressure)	9 (56.2)	34 (58.6)	1	
Urgency	4 (25.0)	13 (22.4)	1.18 (0.27–4.44)	0.818
Both	3 (18.8)	11 (19.0)	1.05 (0.19–4.43)	0.945
Uterus contraction				
No	95 (41.1)	248 (53.7)	1	
Yes	136 (58.9)	214 (46.3)	1.66 (1.20–2.29)	0.002
Dilated cervix status				
Closed	58 (25.1)	310 (67.1)	1	
1–2 cm	173 (74.9)	152 (32.9)	6.06 (4.27–8.70)	0.001

[1)] Univariate logistic regression.
OR, odds ratio.

formed the subgroup analysis to investigate the sensitivity and specificity of the test in each situation. The case group had a significantly higher vaginal fluid creatinine when compared to the control group (median: 0.84 [0.54, 1.22] mg/dL versus 0.09 [0.05, 0.16] mg/dL, p<0.001). In subgroup analysis, patients with dilated cervix tended to have higher vaginal fluid creatinine than those with closed cervix (median: 0.30 [0.11, 0.90] mg/dL versus 0.11 [0.06, 0.22] mg/dL, p<0.001). There were no significant differences between people with and without urinary incontinence (median: 0.16 [0.07, 0.58] mg/dL versus 0.16 [0.06, 0.31] mg/dL, p=0.22). The distribution of vaginal fluid creatinine in each study group and subgroup were visualized in Fig. 1.

ROC curves and Youden's J statistic were used in combination to identify the best cut-off value. The optimal cut-off value for creatinine concentration was 0.29 mg/dL in the general group (including all patients in the study), the closed cervix group, and the group with no urinary incontinence during pregnancy. The dilated cervix group provided a lower cut-off value (0.26 mg/dL) while the urinary incontinence group had a higher cut-off value (0.31 mg/dL). The performance of vaginal fluid creatinine in our study was visualized using the ROC curves for the study population (n=693, Fig. 2), dilated cervix group (n=74, Fig. 3), and urinary incontinence during pregnancy group (n=325, Fig. 4).

Overall, quantitative creatinine in dilated cervix and urinary incontinence groups had lower diagnostic powers compared to the general group. However, the test accuracy, sensitivity, and specificity remain above 90% in all subgroups, with the detailed results presented in Table 4.

Table 3. Multivariate logistic regression analysis for associations between vaginal fluid creatinine and study groups. adjusted for patients characteristics

Factors	Unit	Rude OR	Adjusted OR[1)]	p[1)]
Mother age	Year	0.98 (0.95–1.01)	0.96 (0.89–1.04)	0.35
IUGR	Yes/No	0.55 (0.23–1.28)	2.01 (0.25–16.26)	0.51
Diabetes	Yes/No	0.51 (0.33–0.77)	0.86 (0.34–2.21)	0.76
Urinary incontinence	Yes/No	0.52 (0.29–0.92)	0.01 (0–0.19)	0.001
Term pregnancy (groups)	1/0	0.69 (0.48–0.97)	1.12 (0.43–2.91)	0.82
	≥2/0	0.57 (0.34–0.95)	1.95 (0.53–7.17)	0.31
Gestational age (weeks – groups)	34–41/24–33	1 (0-61-1-63)	0.42 (0.11–1.65)	0.21
Uterus contractions	Yes/No	1.66 (1.21–2.29)	0.8 (0.3–2.1)	0.65
Cervix status	Closed/ Dilated	6.08 (4.26–8.68)	7.59 (2.76–20.88)	<0.001
Creatinine (Log)	1 Log (Creatinine+0.1)	479 (150–1,529)	1,261 (257–6,178)	<0.001

[1)] Multivariate logistic regression.
OR, odds ratio.

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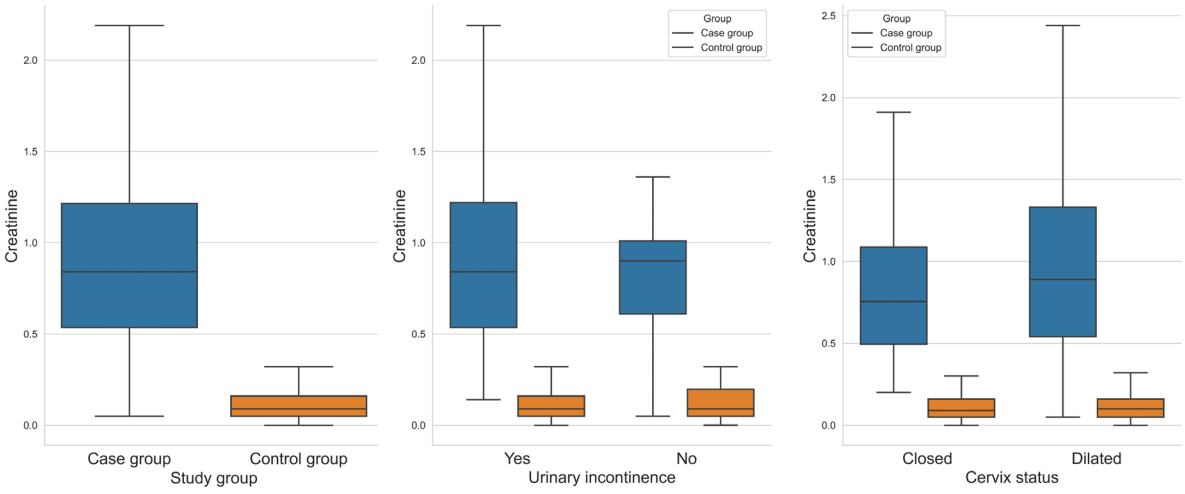

Fig. 1. Distribution of vaginal fluid creatinine in each study group and subgroup analysis.

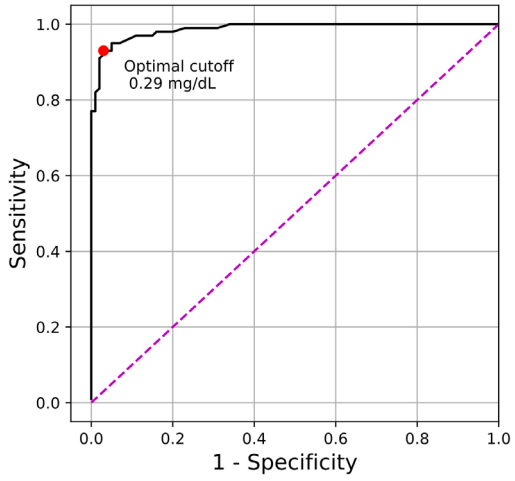

Fig. 2. Receiver operator characteristics (ROC) curve for vaginal fluid creatinine in study population (n=693).

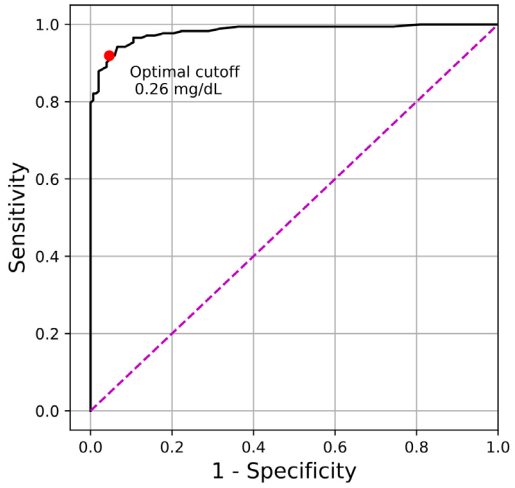

Fig. 3. Receiver operator characteristics (ROC) curve for vaginal fluid creatinine in patients with dilated cervix (n=74).

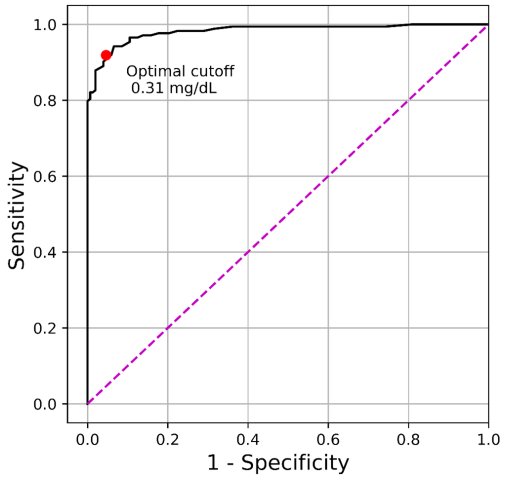

Fig. 4. Receiver operator characteristics (ROC) curve for vaginal fluid creatinine in patients with urinary incontinence during pregnancy (n=325).

4. DISCUSSION

We identified that cervix status and urinary incontinence during pregnancy could be important signs that require doctors' attention. Patients who had a history of urinary incontinence during pregnancy and patients with dilated cervix reduced the sensitivity and specificity of the test and may have altered the cut-off value. However, their diagnostic power remained above 90%.

Creatinine can normally be found in human serum, urine and in amniotic fluid of a fetus. It is believed that the majority of amniotic fluid in the second and third trimester is fetus

Table 4. Diagnostic power of vaginal fluid creatinine in subgroup analysis

Vaginal fluid creatinine (mg/dL)	Ruptured membranes	Intact membranes	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
General (all patients. n=693)					
≥0.29	215	16	0.95 (0.94–0.97)	0.93 (0.89–0.96)	0.97 (0.94–0.98)
<0.29	16	446			
Closed cervix (n=368)					
≥0.29	56	9	0.970 (0.95–0.99)	0.965 (0.88–0.99)	0.971 (0.94–0.99)
<0.29	2	301			
Dilated cervix (n=325)					
≥0.26	163	10	0.94 (0.91–0.96)	0.94 (0.89–0.97)	0.93 (0.88–0.97)
<0.26	10	142			
Urinary incontinence during pregnancy (n=74)					
≥0.31	15	4	0.93 (0.85–0.98)	0.94 (0.70–0.99)	0.93 (0.83–0.98)
<0.31	1	54			
No urinary incontinence during pregnancy (n=619)					
≥0.29	200	12	0.95 (0.93–0.97)	0.93 (0.89–0.96)	0.97 (0.95–0.98)
<0.29	15	392			

urine [12]. When pregnant women had urinary incontinence, it is possible that a small trace of urine can be found in the vagina. This may explain why the diagnostic power of quantitative creatinine in patients with urinary incontinence is lower than in the general population. To the best of our knowledge, we are the first to assess the effect of urinary incontinence on vaginal fluid creatinine. However, the number of patients in the urinary incontinence group in our study is low, therefore, it requires a larger study to confirm this hypothesis.

In our study, patients with a closed cervix were less likely to have ruptured membranes. This finding is similar to Zanjani et al. (2012) [13] and Gezer et al. (2017) [10]. It has been suggested that when the cervix starts dilating, serum compounds can be found in the cervix due to the secretion of damaged tissue [14]. When the membranes remain intact, creatinine is still present in vaginal fluid at a relatively higher concentration than normal. When the membranes rupture, the creatinine in amniotic fluid is diluted with the low-creatinine plasma, reducing the overall creatinine concentration in washing fluid. The combination of these two events could explain the lower cut-off value and diagnostic power of vaginal fluid creatinine test in dilated cervix group versus closed cervix group.

The strengths of our study came from the large sample size and a clear definition for selecting PROM cases. We established a standard operating protocol to collect vaginal fluid for quantitative creatinine tests. This protocol is similar to published studies [13],[15],[16]. The protocol was simple to follow and did not cause any significant changes to our hospital procedures. This provided a foundation for future application in our local facilities, as well as reproducibility in later studies. However, due to constrained resources, there are limitations in this study. Convenience sampling techniques may not provide a presentative sample for the whole population. It is also worth noting that as our hospital served as a referral hospital for an area of more than 10 million people, the prevalence of PROM in our hospital might be higher than in the general population. As we relied on both medical records and patients' memory for their medical history, recall bias might affect our results.

5. CONCLUSION

Our study once again confirmed the significant difference in creatinine levels in vaginal fluid between ruptured and unruptured membranes in pregnant women. Establishing the quantity of creatinine levels in the vaginal fluid is a minimally invasive test that comes with an affordable price, high diagnostic power, and is easy to implement into existing infrastructure at local hospitals. This is why quantitative creat-

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inine in the vaginal fluid has the potential to become a good test for diagnosing PROM, especially in low-and-middle-income-countries. Doctors should be careful in complicated cases, paying attention to the patient's history and conducting a thorough examination to note the urinary incontinence history and cervix status, as these two factors might alter the diagnostic power of the quantitative creatinine in the vaginal fluid test.

Although our study provided a positive result on the usage of quantitative creatinine in vaginal fluid, obstetrics should remain vigilant about the strengths and limitations of this test in clinical application. It should be noted that the sample size for subgroup analysis, especially the urinary incontinence group, is relatively small and might not be statistically sufficient. Future studies can look deeper into this topic to investigate which group of patients can receive the most benefit from this test. Further studies that compare the diagnostic power of quantitative creatinine to other commercially available, FDA-approved diagnostic tests such as PMAG-1, will be beneficial to both researchers and clinicians. Finally, developing a point-of-care test based on quantitative and qualitative creatinine that is simple to use and provides rapid results for detecting PROM would be beneficial in resource-constrained settings.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Writing - review & editing: TM Vo, TV Ho, MTN Do, DNY Dang, YNH Le.

Availability of data and material

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics approval

The study protocol was reviewed and approved by the Hung Vuong hospital ethics committee (reference number 1868/HĐĐĐ-BVHV). All pregnant women who participated in the study had been consulted and provided written informed consent.

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