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Original Research

Assessment of Soluble Intercellular Adhesion Molecule-1 Based Rapid Test for a Quick Diagnosis of Atypical Prelabor Rupture of Membranes in the Emergency Setting

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Abstract

Background: There is an urgent need to evaluate the clinical value of soluble intercellular adhesion molecule-1 (sICAM-1) based rapid tests (Leakection) for a quick and relatively accurate diagnosis of prelabor rupture of membranes (PROM), especially atypical PROM, in the emergency setting. This is a retrospective study. The data collection was planned after all the index test and reference standard were performed retrospectively. **Methods**: A total of 267 pregnant women complaining of increased vaginal effusion were recruited. For preliminary diagnoses, patients were examined by observing posterior vault pooling and by performing nitrazine tests and Leakection tests. PROM was subsequently confirmed with a clinical diagnosis consisting of both patient history and the results of a panel of tests. The sensitivity and specificity of posterior vault pooling, Leakection from the posterior vault and the nitrazine test in the emergency setting were retrospectively reported to evaluate their power of diagnosis in PROM. **Results**: One hundred thirty-two patients were diagnosed with PROM, and 135 patients were found not to have PROM. When samples were collected from the posterior vault, Leakection had a sensitivity of 97.0%, a specificity of 91.1%, and a false negative rate of 3.0%. In contrast, the nitrazine test had a sensitivity of 68.9%, a specificity of 100.0%, and a false negative rate of 31.1%. **Conclusions**: Leakection is a noninvasive and inexpensive rapid test for the screening and diagnosis of PROM with both high sensitivity and specificity. This test can greatly aid in the clinical diagnosis of PROM, especially atypical PROM, in the emergency setting.

Keywords: emergency; Leakection; prelabor rupture of membrane; soluble intercellular adhesion molecule-1

1. Introduction

Prelabor rupture of membranes (PROM) is the rupture of the fetal membranes and leakage of amniotic fluid before the onset of labor. The incidence rate of PROM is about 6–19% of term pregnancies, with the high risk of perinatal and neonatal complications [1]. The clinical management of women with PROM remains challenging. When vaginal pooling of amniotic fluid, vernix, or meconium is observed at speculum examination, the diagnosis is easy and straight forward [2]. However, in pregnant women with increased vaginal fluid but no obvious pooling, the diagnosis of PROM requires lab tests for confirmation or exclusion [3]. Multiple tests could be used, including nitrazine paper, the fern test, and ultrasound examination, all of which are traditionally and widely used [3]. More recently, immunoassays detecting proteins in amniotic fluid have been developed and reported to be quick and accurate. These proteins are considered biomarkers for PROM, including soluble intercellular adhesion molecule-1 (sICAM-1) [4,5], insulin-like growth factor binding protein-1 [6–8], and placental alpha microglobulin-1 [6–9]. These point-of-care immunoassays can detect trace amounts of leaked amniotic fluid, and therefore are assumed to be especially useful for a quick and preliminary diagnosis for a patient presenting at the emergency room.

sICAM-1 as a biomarker for PROM was originally discovered at our hospital, and then developed into a bedside rapid strip test with the name of Leakection. It is reported to be sensitive and specific, and clinically useful for detecting PROM [4,5]. In this study we conducted a real-world assessment of this test for use at emergency to detect atypical PROM, pregnant women complaining of increased vaginal fluid but with no obvious pooling. For the purpose of reaching a quick decision at emergency, we included observation of amniotic fluid and the nitrazine test as reference examinations, but excluded assays that are time-consuming including fern test and ultrasound examination. We hope to illuminate a noninvasive and inexpensive rapid test for the screening and diagnosis of PROM, especially in atypical PROM, through a test with high sensitivity and specificity.

Table 1. Clinical Characteristic of the Study Subjects.

	PROM (n = 132)	95% CI	Non-PROM (n = 135)	95% CI
Maternal Age (Year)				
Mean ± SD	30.46 ± 3.90	30.46 ± 0.65	31.17 ± 3.46	31.17 ± 0.59
Range	20–39		25–39	
Gestational Age at Sample Collection (Week^{+Day})				
Mean ± SD	35.33 ± 6.05	35.33 ± 1.12	34.22 ± 7.37	34.22 ± 1.26
Range	17–40^{+6}		14–40^{+6}	

PROM, prelabor rupture of membranes; CI, confidence interval; SD, standard deviation.

2. Materials and Methods

2.1 Study Design

The data collection was planned after all the index test and reference standard were performed retrospectively.

2.2 Subjects

Eligibility criteria: pregnant women who complained increased vaginal effusion when they consult in our emergency room (from 24 March 2022 to 30 August 2022 consecutively), excluded those who have vaginal bleeding, vaginal pooling of amniotic fluid or vernix or meconium in effusion. The research design was approved by the Institutional Review Board of West China Second University Hospital, Sichuan University, and informed consent was signed by all patients. A total of 267 pregnant women were recruited. All participants were predominantly originated from the Han Chinese. Each woman was examined by speculum examination for posterior vault pooling, nitrazine test, and Leakection on samples separately collected from the posterior vault and vagina. The detailed patient demography is presented in Table 1. PROM was diagnosed according to the initial preliminary screening done in the emergency setting and the follow-up results of the inpatient department and outpatient department (Fig. 1). The following diagnostic standard according to our clinical practice in West China Second University Hospital and the *Textbook of Obstetrics and Gynecology* of China and the guideline of PROM from Society of Obstetricians and Gynaecologists of Canada (SOGC) and American College of Obstetricians and Gynecologists (ACOG) was used as showed in Fig. 1: (1) Vaginal pooling of amniotic fluid, (2) Vernix or meconium is observed, (3) positive nitrazine test (inpatient department re-test result), (4) positive crystallization test, (5) decreased amount of amniotic fluid at ultrasound examination; (1)+(2)/(3)/(4)/(5) or (3)+(4)+(5) at inpatient department was diagnosed as PROM. All data were collected from our HIS system and no missing happened in all participants.

2.3 Nitrazine Test

A nitrazine test paper was placed at the posterior vault for approximately 5 seconds on a pregnant woman at speculum examination. Test paper that changes to blue is considered a positive result, suggesting the occurrence of PROM.

2.4 Leakection Test

Posterior vault and vaginal fluid samples were collected separately from each patient to avoid visible blood contamination. The posterior vault sample was collected underneath the posterior cervical lip, and the vaginal sample was collected 3–5 cm inward the vagina. The Leakection test was performed according to previous work [4,5]. Briefly, the samples were collected and added into the sample well of the Leakection test card (Origissay Diagnostic, Ltd., Chengdu, Sichuan, China). The results were observed within 3–5 minutes, with the presence of the test line and control line being interpreted as a positive result for PROM while the presence of the control line but not the test line being interpreted as a negative result for PROM.

2.5 Statistical Analysis

The sample size was based on the primary endpoint. Assuming a clinical requirement of 90% test accuracy, the test is expected to be 95% accuracy. To detect this different between the test and the margin of clinical requirement with 90% power with a two-sided significance level of 5%, our research required more than 239 patients (PASS 15.0, Number Cruncher Statistical System, Atlanta, GA, USA). The number of patients diagnosed with PROM as well as those found to be negative for PROM was counted. Sensitivity, specificity, positive predictive value, negative predictive value, validity, false positive diagnostic rate, and false negative diagnostic rate of the test were calculated using the algorithm reported in previous work [4,5].

3. Results

Totally, 267 pregnant women who presented at the emergency room complaining of increased vaginal fluid but with no obvious pooling, and therefore suspected of PROM, were tested in this real-world study. Following the initial assessment in the emergency room, 132 patients were confirmed to have PROM, and 135 patients were confirmed to not have PROM. The results are presented in Table 2. Posterior vault pooling was observed in 92/132 (69.7%) of the patients diagnosed with PROM and in 9/135 (6.7%) of the patients that were found to not have PROM. The nitrazine test was positive in 91/132 (68.9%) of the patients diagnosed with PROM and 0/135 (0%) of the patients that

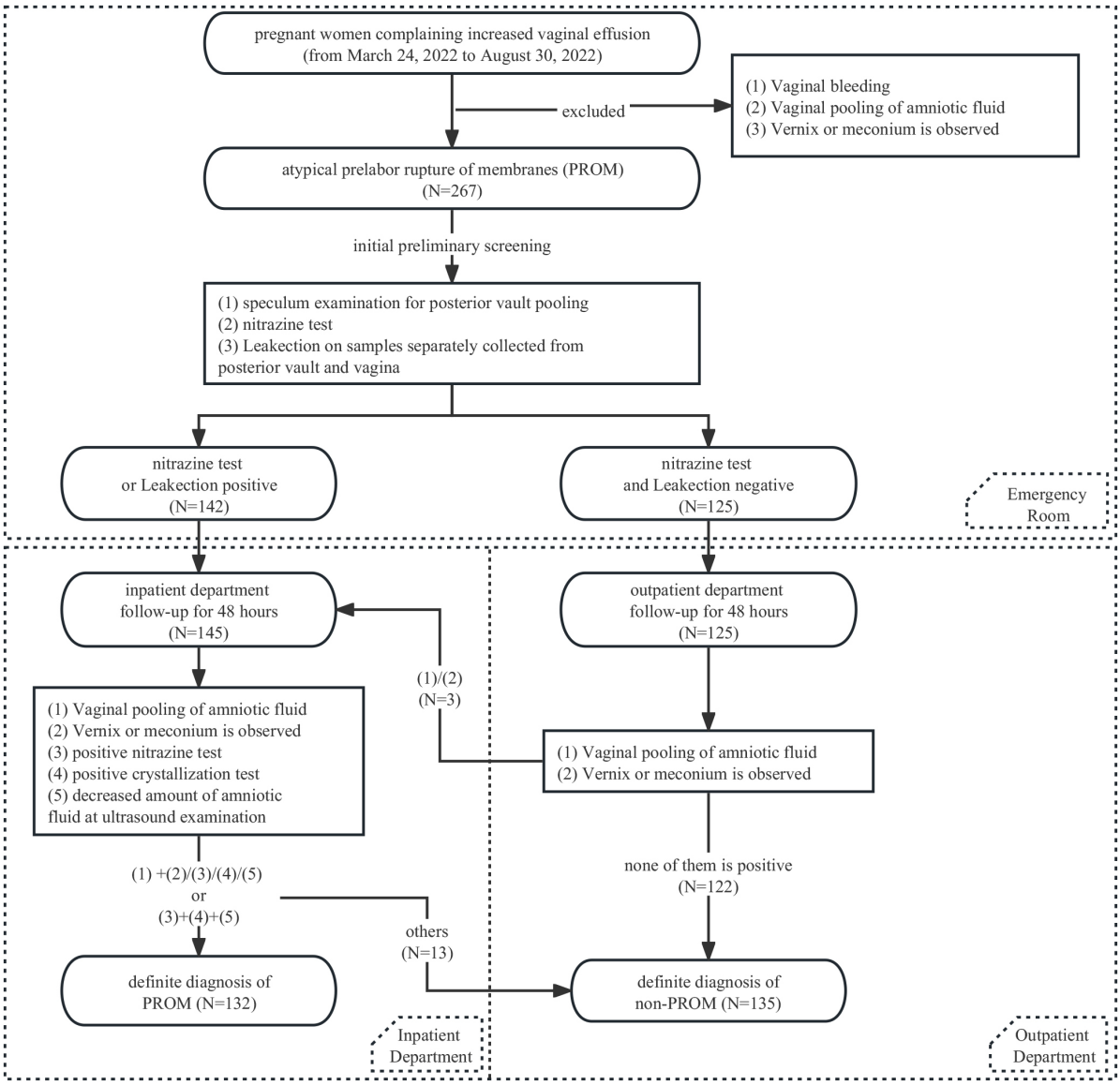

Fig. 1. Definite diagnosis of prelabor rupture of membranes (PROM) and non-PROM in the study.

were found to not have PROM. The above two exams overlapped in the PROM, as only in those patients having posterior vault pooling the nitrazine test was positive. Leakection examining the posterior vault samples was positive in 128/132 (97.0%) of the patients diagnosed with PROM and in 12/135 (8.9%) of the patients that were found to not have PROM. Leakection examining the vaginal samples was positive in 115/132 (87.1%) of the patients diagnosed with PROM and in 7/135 (5.2%) of the patients that were found to not have PROM.

Leakection had a high sensitivity and specificity, and the samples collected from the posterior vault showed a higher sensitivity (97.0% *vs.* 87.1%) and a similar specificity (91.1% *vs.* 94.8%) compared to the samples collected from the vagina. Although observation of posterior vault pooling and the nitrazine test had a high specificity (93.3% and 100%), their low sensitivity (69.7% and 68.9%) led to a high false negative diagnostic rate (30.3% and 31.1%). In contrast, Leakection had a low omission diagnostic value, especially when tested on samples collected from the posterior vault (3.0%) (Table 3).

Sixteen cases were revealed to be weakly positive by Leakection on posterior vault samples, and 10 were confirmed to be PROM, and 6 were non-PROM. Twenty cases were revealed to be weakly positive by Leakection on vaginal samples, 14 were confirmed to be PROM, and 6 were non-PROM. The mistaken diagnosis rate of Leakection examination was therefore mainly contributed by the weak positive cases.

4. Discussion

To date, the gold standard for PROM diagnosis is instillation of indigo carmine dye into the amniotic cavity, which is invasive and very hard for routinely clinical use

Table 2. Test Results of Posterior Vault Pooling, Nitrazine Test and Leakection Examination.

	Posterior vault pooling		Nitrazine test		Leakection			
					Posterior vault sample		Vagina sample	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
PROM (n = 132)	92	40	91	41	128	4	115	17
Non-PROM (n = 135)	9	126	0	135	12	123	7	128

PROM, prelabor rupture of membranes.

Table 3. Diagnostic value of Posterior Vault Pooling, Nitrazine Test and Leakection Examination.

	Posterior vault pooling	Nitrazine test	Leakection	
			Posterior vault sample	Vaginal sample
Sensitivity	69.7	68.9	97.0	87.1
Specificity	93.3	100	91.1	94.8
Positive predictive value	91.1	100	91.4	94.3
Negative predictive value	78.5	76.7	96.9	88.3
Validity	81.6	84.6	94.0	91.0
False positive diagnostic rate	6.7	0	8.9	5.2
False negative diagnostic rate	30.3	31.1	3.0	12.9

[10–13]. In this study, a clinical working diagnosis was adopted in the emergency setting following a thorough collection of patient history, physical examination of the patient for visible pooling of amniotic fluid in the posterior vault, and additional tests: nitrazine tests, crystallization tests with ferning pattern, and ultrasound examinations.

In this clinical study of patients presenting at the emergency room, we assessed the efficacy of the rapid tests including observation of posterior vault pooling, the nitrazine test and Leakection for a quick and preliminary differentiation between patients likely to have PROM and those who do not.

sICAM was previously reported as a useful biomarker for the diagnosis of PROM with a high sensitivity and specificity [4,5], which has been developed into bedside rapid test tool named Leakection. The clinical value of Leakection, especially when a quick decision has to be made, was again revealed in the current study, with the sensitivity and specificity of 97.0% and 91.1%, respectively in this real-world assessment, similar to the results previously reported [4,5]. The other two indicators used in this assessment were observation of posterior vault pooling and the nitrazine test; both were highly specific but low in sensitivity (69.7% and 68.9%). This low sensitivity suggests these methods are inadequate to quickly and accurately screen for PROM. Other noninvasive and inexpensive products, such as Amnioquick and Leakection were reported to have high sensitivity and specificity, while Leakection provides higher sensitivity and specificity [14]. Taken together, we may conclude that Leakection might be a rapid test for aiding with the initial and perhaps final diagnosis of PROM, especially for atypical PROM, and especially at a busy emergency department, and/or at hospitals with expertise and sophisticated equipment unavailable.

For the Leakection test a small percentage of patients showed weakly positive results. Of the samples collected in both ways, 60–70% of these weakly positive patients turned out to be having PROM. Therefore, when observing weak positivity from the Leakection test, it is important to follow up with additional testing prior to diagnosis.

Sampling from the posterior vault was revealed to have a much higher sensitivity compared to sampling from the vagina. It has been suggested that at a clinic samples collected from the posterior vault should always be used for Leakection testing. Nevertheless, sampling from the vagina is easier to conduct, and this sampling method may be utilized by pregnant women to test at home when considered at high risk for PROM. If positive by self-test, the pregnant woman should go to a hospital for confirmation and potential intervention to treat PROM.

5. Conclusions

In conclusion, in this real-world study at a busy emergency department, we found that Leakection for screening PROM is both highly sensitive and specific and has an omission diagnostic value as low as 3%. Because of the advantage of Leakection compared to posterior vault pooling and nitrazine tests, we suggest that Leakection be used as the primary choice for PROM screening in the emergency setting, and in particular for detecting atypical PROM.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

LT—extraction and drafting of the manuscript, statistical analysis; XL—analysis of data, manuscript revision; YH and ZZ—design and revision. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Institutional Review Board of West China Second University Hospital, Sichuan University (approval number: 2018YFC1004603).

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Medina TM, Hill DA. Preterm premature rupture of membranes: diagnosis and management. American Family Physician. 2006; 73: 659–664.

[2] El-Messidi A, Cameron A. Diagnosis of premature rupture of membranes: inspiration from the past and insights for the future. Journal of Obstetrics and Gynaecology Canada. 2010; 32: 561–569.

[3] Menon R, Richardson LS. Preterm prelabor rupture of the membranes: A disease of the fetal membranes. Seminars in Perinatology. 2017; 41: 409–419.

[4] Wang T, Zhou R, Zhang L, Wang Y, Song CP, Lin W, *et al*. Proteins in leaked amniotic fluid as biomarkers diagnostic for prelabor rupture of membranes. Proteomics. Clinical Applications. 2011; 5: 415–421.

[5] Wang T, Zhou R, Xiong W, Wang Y, Zhu C, Song C, *et al*. Clinical evaluation of soluble intercellular adhesion molecule-1 and insulin like growth factor-binding protein-1-based rapid immunoassays for the diagnosis of prelabor rupture of membranes. Journal of Perinatal Medicine. 2013; 181: 5–9.

[6] Tagore S, Kwek K. Comparative analysis of insulin-like growth factor binding protein-1 (IGFBP-1), placental alpha-microglobulin-1 (PAMG-1) and nitrazine test to diagnose premature rupture of membranes in pregnancy. Journal of Perinatal Medicine. 2010; 38: 609–612.

[7] Albayrak M, Ozdemir I, Koc O, Ankarali H, Ozen O. Comparison of the diagnostic efficacy of the two rapid bedside immunoassays and combined clinical conventional diagnosis in prelabour rupture of membranes. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2011; 158: 179–182.

[8] Chen FCK, Dudenhausen JW. Comparison of two rapid strip tests based on IGFBP-1 and PAMG-1 for the detection of amniotic fluid. American Journal of Perinatology. 2008; 25: 243–246.

[9] Phupong V, Sonthirathi V. Placental alpha-microglobulin-1 rapid immunoassay for detection of premature rupture of membranes. The Journal of Obstetrics and Gynaecology Research. 2012; 38: 226–230.

[10] Pinar H, Sotomayor E, Singer DB. Pathological case of the month. Turquoise discoloration of the umbilical cord and membranes after intra-amniotic injection of indigo carmine dye for premature rupture of membranes. Archives of Pediatrics & Adolescent Medicine. 1998; 152: 199–200.

[11] Eden E, Insler V, Serr DM. Diagnosis of premature rupture of the fetal membranes by intra-amniotic dye injection. Harefuah. 1976; 91: 275–276.

[12] Davidson KM. Detection of premature rupture of the membranes. Clinical Obstetrics and Gynecology. 1991; 34: 715–722.

[13] Gorodeski IG, Haimovitz L, Bahari CM. Reevaluation of the pH, ferning and nile blue sulphate staining methods in pregnant women with premature rupture of the fetal membranes. Journal of Perinatal Medicine. 1982; 10: 286–292.

[14] Wang T, Zhou R, Xiong W, Wang Y, Zhu C, Song C, *et al*. Clinical evaluation of soluble intercellular adhesion molecule-1 and insulin like growth factor-binding protein-1-based rapid immunoassays for the diagnosis of prelabor rupture of membranes. Journal of Perinatal Medicine. 2013; 41: 181–185.