Diagnostic Modalities in Premature Rupture of Membranes

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Abstract

Objectives: Rupture of membranes prior to the onset of labor is known as Premature Rupture of Membranes (PROM). Early and correct diagnosis is crucial in order to prevent fetal and maternal risks that can be life threatening. We aimed to investigate the diagnostic ability of the tests in PROM.

Materials and Methods: Nitrazine test, fern test, amnio-dye test, biochemical tests (insulin-like growth factor binding protein-1 and placental alpha microglobulin-1) were evaluated in terms of effectiveness in diagnosis of PROM.

Results: A gold standard method has not yet been defined in PROM. Diagnostic tests (nitrazine test, fern test, Insulin-like Growth Factor Binding Protein-1 “IGFBP-1” and Placental Alpha Microglobulin-1 ”PAMG-1”) should be used when the diagnosis is not certain following history, examination with sterile speculum and ultrasonography evaluation.

Conclusion: IGFBP-1 and PAMG-1 are tests based on bedside immunochromatographic method. Especially, PAMG-1 comes into prominence with its high sensitivity and specificity.

Keywords: Fetal membranes, Insulin-like growth factor binding protein 1, Placental alpha-microglobulin 1, Premature rupture

Introduction

Premature Rupture of Membranes (PROM) is defined as rupture of membranes prior to onset of labor. It can occur at any gestational week. PROM greater than 24 hours is referred as prolonged PROM and carries risk of ascending infection (1). PROM occurs in 8%-10% of all term pregnancies and in 2%-4% of all preterm singleton pregnancies (1,2). The most important maternal risk is intrauterine infection that increases with the time till onset of labor. Primary fetal risks associated with PROM include compression of umbilical cord secondary to oligohydramnios and ascending infection. Preterm PROM carries four-fold increased risk of fetal mortality, while there is a three-fold increase in risk of morbidity including intraventricular hemorrhage and respiratory distress syndrome in addition to ascending infection (1-3).

In order to prevent all these complications, early and certain diagnosis of PROM is important in terms of performing intervention to minimize adverse outcomes. On the contrary, a false positive diagnosis causes unnecessary hospitalization, obstetric intervention, treatments such as steroids and even preterm induction of labor (1,2,4,5).

Materials and Methods

Nitrazine test, fern test, amnio-dye test, biochemical tests (Placental Alpha Microglobulin-1 “PAMG-1” and Insulin-like Growth Factor Binding Protein-1 “IGFBP-1”) were evaluated in terms of effectiveness (sensitivity, specificity, positive predictive value, negative predictive value) in the diagnosis of PROM.

Results

Clinical signs are commonly used in the diagnosis of PROM. Description of vaginal fluid flow is typical in the medical history. Amniotic fluid flow can be observed through vaginal speculum. Diagnosis of PROM can be made by showing the three gold standards of conventional findings by a clinician (1);

1. Observation of clear amniotic fluid flow or accumulation of fluid at posterior fornix with a sterile speculum,
2. Observation of transition from yellow to blue with pH indicator paper due to basic amniotic fluid flow (nitrazine test) and/or,

Presence of oligohydramnios detected by Leopold maneuvers and/or ultrasonography also supports the diagnosis (1).

Nitrazine test

It is applied with nitrazine paper treated with dinitrophenylxlo naphthalene disulfonic acid. This test, used for the first time by Bamptisti in 1938, is based on the fact that
acidi c vaginal pH (pH<4.5) becomes basic (pH: 7.1-7.3) with amniotic fluid flow. If pH of nitrazine paper is >6.4, it turns to blue. False positivity is caused by infection (vaginitis, cervicitis) as well as contamination with blood, semen and antiseptic solution (1,6,7). Sensitivity of this test ranges between 90% to 97% and specificity ranges from 16%-70% (8,9).

Fern test
It was described by Papanicalou in 1946. It is characterized by formation of “palm leaf-pattern” in dried cervical mucus when it is smeared over glass slide due to its NaCl and protein content. Immersion with cervical mucus, semen and finger contamination can affect the accuracy of the test. Sensitivity of this test ranges between 51%-98% and specificity ranges from 70%-78% (10,11).

Amnio-dye test
Diagnosis with conventional methods becomes generally difficult if more than 1 hour has passed following the amniotic fluid flow (1). Concern about meeting possible adverse outcomes without a diagnosis or unnecessary intervention because of false diagnosis can require use of invasive methods. In amnio-dye test (also known as Tampon test) indigo carmine is injected into amniotic cavity via amnio-infusion. Dying of tampon in the vagina is evaluated after 20-30 minutes. Although it is described as gold standard diagnostic method by some authors, this invasive test carries risks such as ablation placenta, iatrogenic PROM, infection and pregnancy loss (12). Since methylene blue can cause methemoglobinemia, it is not used for dying (13).

Biochemical tests
Limited possibilities of the aforementioned test directed the researchers to look for new tests. An ideal test should be rapid, accurate, noninvasive, inexpensive, easily-applicable, and available in cervicovaginal secretions when rupture of membranes has occurred, whereas it should be absent in case of intact membranes. This search enabled conducting studies on fetal fibronectin (fFN), IGFBP-1, Alpha Fetoprotein (AFP), beta-subunit of human chorionic gonadotropin (β-hCG), prolactin, creatinine, urea, lactate, and PAMG-1 (14-20). Recently IGFBP-1 and PAMG-1 are included in popular diagnostic methods as simple bedside tests. These tests are based on detection of relevant proteins in cervicovaginal fluids (21-23). IGFBP-1 is a major insulin-like growth factor binding protein. During second trimester of pregnancy, its concentration increasingly enhances and reaches rather high levels compared to maternal plasma (23-25). Its concentration is 100-1000 times more in amniotic fluid than in other body fluids (25). The phosphorylated isoform is secreted mainly from the decidual cells and the liver, while the nonphosphorylated isoform is present mainly in amniotic fluid (24,25). Semen and urine contamination do not interfere with test results, however large amount of blood can cause false positivity (26,27).

PAMG-1 has a concentration of 2000-25000 ng/ml in amniotic fluid, whereas its concentration in maternal blood is 5-25 ng/ml. Its concentration in cervicovaginal secretion is below 0.05-0.2 ng/ml in case of intact membranes (20,28). 1000-10000-fold difference between amniotic fluid and cervicovaginal secretions puts this test forward. When the threshold value is taken as 5 ng/ml, it can detect PROM with 99% accuracy. It does not exceed 5 ng/ml even in case of vaginal infection or contamination with blood (29). In a study of 184 patients with PROM symptoms, sensitivity, specificity, positive and negative predictive value were 99%, 88%, 98%, and 91%, respectively (30).

Discussion
IGFBP-1 and PAMG-1 are used as practical tests working with immunochromatographic method. Monoclonal antibody gives rapid and easily interpretable result by binding with IGFBP-1 or PAMG-1 in vaginal smear. They are rapid tests consisting of a swap (cotton stick) to obtain amniotic fluid sample, a bottle of solvent (solvent that enables extrication of the sought substance in amniotic fluid) and test kit. Swap is kept in vagina for one minute and when kept in the solvent for another minute, molecule is extricated. Result can be obtained in 5 to 10 minutes by soaking the test kit in the solvent. No appearance of control line can be interpreted as “invalid”, single line (control) as “negative” and double line (control and test lines) as “positive” easily and rapidly in 10 minutes (12,26,27) (Figure 1).

In a meta-analysis that evaluated the accuracy differences between IGFBP-1 and PAMG-1 (31), it was claimed that PAMG-1 was a more reliable test that could be used between 11-42 weeks of gestation. Sensitivity and specificity for IGFBP-1 in same patient groups were 96% and 73.9%, respectively, while for PAMG-1, those values were 98.9% and 77.8%, respectively (31). However, it was emphasized that there was not any significant difference between IGFBP-1 and PAMG-1 in studies done during the period following meta-analysis. It was reported that they both were easy, rapid and simple bedside tests (21,22). Cut off values and diagnostic performances of noninvasive diagnostic tests used in PROM diagnosis by some investigators are presented in Table 1.

Conclusion
Accuracy of PROM diagnosis is vital both for the moth-
er and fetus. A golden standard method has not yet been defined in PROM. Diagnostic tests should be used when the diagnosis is not certain following history, examination with sterile speculum and ultrasonography evaluation. Among biochemical tests, PAMG-1 and IGFBP-1 have the features of being easily applicable tests. PAMG-1 comes into prominence with its high sensitivity and specificity. Results of tests used in PROM diagnosis must be supported by clinical findings.

Ethical issues
Not applicable.

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Conflict of interests
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