http://www.ijwhr.net
doi 10.15296/ijwhr.2015.17
Open Access Original Article
IJWHR
International Journal of Women's Health and Reproduction Sciences
Vol. 3, No. 2, April 2015, 89–92
ISSN 2330-4456

Diagnostic Modalities in Premature Rupture of Membranes

Fatma Eskicioglu[1*], Esra Bahar Gur[2]

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,
3. Detection of palm leaf-pattern in dried amniotic fluid with microscopic method (fern test).

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 dinitrophenyloxo naphthalene disulfonic acid. This test, used for the first time by Bamptisti in 1938, is based on the fact that

Received 15 October 2014, **Accepted** 6 February 2015, **Available online** 14 February 2015

[1]Department of Obstetrics and Gynecology, School of Medicine, Celal Bayar University, Manisa, Turkey. [2]Department of Obstetrics and Gynecology, School of Medicine, Sifa University, Izmir, Turkey.
***Corresponding author:** Fatma Eskicioğlu, Department of Obstetrics and Gynecology, School of Medicine, Celal Bayar University, Manisa, Turkey. Tel: +90(505)2595349, Email: fatmaeskicioglu@gmail.com

acidic 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-

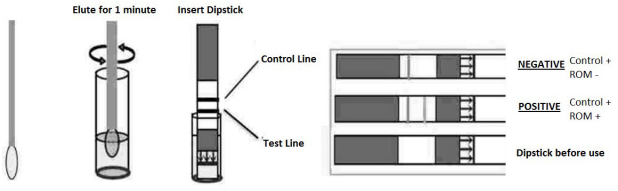

Figure 1. The use of test describes. Result can be obtained in 5 to 10 minutes by soaking the test kit in the solvent. No appearance of control line can be interpreted as "invalid", single line (control) as "negative" and double line (control and test lines) as "positive".

Table 1. Diagnostic performance of noninvasive tests in rupture of the fetal membranes

Test/Reference	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Nitrazine (pH) (6,8,9)	Positive/negative	90-97	16-70	63-75	80-93
Ferning (6,7,10)	Positive/negative	51-98	70-88	84-93	87-97
IGFBP-1 (8,9,17,31)	> 3 µg/L	74-97	74-97	73-92	56-87
PAMG-1 (20,29-31)	> 5.0 ng/mL	96-99	88-100	98-100	91-99

IGFBP-1: Insulin like Growth Factor Binding Protein 1; PAMG-1: Placental alpha-microglobulin 1; NPV: Negative Predictive Value; PPV: Positive Predictive Value.

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.

Financial support

The author(s) received no financial support for the research, authorship and/or publication of this article.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

We have no acknowledgements to disclose.

References

1. ACOG Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 80: premature rupture of membranes. Clinical management guidelines for obstetrician-gynecologists. Obstet Gynecol 2007;109(4):1007-19. doi: 10.1097/01.aog.0000263888.69178.1f
2. [No authors listed]. ACOG practice bulletin. Premature rupture of membranes. Clinical management guidelines for obstetrician-gynecologists. Number 1, June 1998. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 1998;63(1):75-84.
3. Dale PO, Tanbo T, Bendvold E, Moe N. Duration of the latency period in preterm premature rupture of the membranes. Maternal and neonatal consequences of expectant management. Eur J Obstet Gynecol Reprod Biol 1989;30(3):257-62. doi: 10.1016/0028-2243(89)90010-5
4. Hannah ME, Hodnett ED, Willan A, Foster GA, Di Cecco R, Helewa M. Prelabor rupture of the membranes at term: expectant management at home or in hospital? The Term PROM Study Group. Obstet Gynecol 2000;96(4):533-8.
5. Healy AJ, Veille JC, Sciscione A, McNutt LA, Dexter SC; Society of Maternal-Fetal Medicine. The timing of elective delivery in preterm premature rupture of the membranes: a survey of members of the Society of Maternal-Fetal Medicine. Am J Obstet Gynecol 2004;190(5):1479-81.
6. 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. J Perinat Med 1982;10(6):286-92. doi: 10.1515/jpme.1982.10.6.286
7. de Haan HH, Offermans PM, Smits F, Schouten HJ, Peeters LL. Value of the fern test to confirm or reject the diagnosis of ruptured membranes in modest in nonlaboring women presenting with nonspecific vaginal fluid loss. Am J Perinatol 1994;11(1):46-50. doi: 10.1055/s-2007-994535
8. Gaucherand P, Salle B, Sergeant P, Guibaud S, Brun J, Bizollon CA, et al. Comparative study of three vaginal markers of the premature rupture of membranes. Insulin like growth factor binding protein, 1 diamineoxidase, and pH. Acta Obstet Gynecol Scand 1997;76(6):536-40. doi: 10.3109/00016349709024579
9. Erdemoglu E, Mungan T. Significance of detecting insulin-like growth factor binding protein1 in cervicovaginal secretions: comparison with nitrazine test and amniotic fluid volume assessment. Acta Obstet Gynecol Scand 2004;83(7):622-6. doi: 10.1080/j.0001-6349.2004.00343.x
10. Rosemond RL, Lombardi SJ, Boehm FH. Ferning of amniotic fluid contaminated with blood. Obstet Gynecol 1990;75 (3 Pt 1):338-40.
11. Smith RP. A technique for the detection of rupture of the membranes: a review and preliminary report. Obstet Gynecol 1976;48(2):172-6.
12. Caughey AB, Robinson JN, Norwitz ER. Contemporary diagnosis and management of preterm premature rupture of membranes. Rev Obstet Gynecol 2008;1(1):11-22.
13. Spahr RC, Salsburey DJ, Krissberg A, Prin W. Intraamniotic injection of methylene blue leading to methemoglobinemia in one of twins. Int J Gynaecol Obstet 1980;17(5):477-8.
14. Li HY, Chang TS. Vaginal fluid creatinine, human chorionic gonadotropin and alpha-fetoprotein levels for detecting premature rupture of membranes. Zhonghua Yi Xue Za Zhi (Taipei) 2000;63(9):686-90.
15. Shahin M, Raslan H. Comparative study of three amniotic fluid markers in premature rupture of

membranes: prolactin, beta subunit of human chorionic gonadotropin, and alpha-fetoprotein. Gynecol Obstet Invest 2006;63(4):195-9.
16. Lockwood CJ, Senyei AE, Dische MR, Casal D, Shah KD, Thung SN, et al. Fetal fibronectin in cervical and vaginal secretions defines a patient population at high risk for preterm delivery. N Engl J Med 1991;325(10):669-74. doi: 10.1056/nejm199109053251001
17. Jeurgens-Borst AJ, Bekkers RL, Sporken JM, van der Berg PP. Use of insulin like growth factor binding protein-1 in the diagnosis of ruptured fetal membranes. Eur J Obstet Gynecol Reprod Biol 2002;102(1):11-4. doi: 10.1016/s0301-2115(01)00560-7
18. Kafali H, Oksuzler C. Vaginal fluid urea and creatinine in diagnosis of premature rupture of membranes. Arch Gynecol Obstet 2007;275(3):157- 60. dx.doi.org/10.1007/s00404-006-0240-1
19. Wiberg-Itzel E, Cnattingius S, Nordstrom L. Lactate determination in vaginal fluids: a new method in the diagnosis of prelabour rupture of membranes. BJOG 2005;112(6):754-8.
20. Petrunin DD, Griaznova IM, Petrunina IuA, Tatarinov IuS. Immunochemical identification of organ specific human placental alphaglobulin and its concentration in amniotic fluid. Akush Ginekol (Mosk) 1977;(1):62-4. [in Russian]
21. Abdelazim IA, Makhlouf HH. Placental alpha microglobulin-1 (AmniSure test) versus insulin-like growth factor binding protein-1 (Actim PROM test) for detection of premature rupture of fetal membranes. J Obstet Gynaecol Res 2013;39(6):1129-36. doi: 10.1111/jog.12045
22. Doret M, Cartier R, Miribel J, Massardier J, Massoud M, Bordes A, et al. Premature preterm rupture of the membrane diagnosis in early pregnancy: PAMG-1 and IGFBP-1 detection in amniotic fluid with biochemical tests. Clin Biochem 2013;46(18):1816-9. doi: 10.1016/j.clinbiochem.2013.10.006
23. Julkunen M, Koistinen R, Aalto-Setälä K, Seppälä M, Jänne OA, Kontula K. Primary structure of human insulin-like growth factor binding protein/ placental protein 12 and tissue expression of its mRNA. FEBS Lett 1988;236(2):295-302.
24. Rutanen EM, Bohn H, Seppala M. Radioimmunoassay of placental protein 12: levels in amniotic fluid, cord blood, and serum of healthy adults, pregnant women and patients with trophoblastic diseases. Am J Obstet Gynecol 1982;144(4):460-3.
25. Martina NA, Kim E, Chitkara U, Wathen NC, Chand T, Giudice LC. Gestational age-dependent expression of insulin-like growth factor binding protein (IGFBP-I) phospho-forms in human extra-amniotic cavities, maternal serum, and decidua suggests decidua as the primary source of IGFBP-I in these fluids during early pregnancy. J Clin Endocrinol Metab 1997;82(6):1894-8.
26. Medina TM, Hill DA. Preterm premature rupture of membranes: diagnosis and management. Am Fam Physician 2006;73(4):659-64.
27. Ting HS, Chin PS, Yeo GS, Kwek K. Comparison of bedside test kits for prediction of preterm delivery: phosphorylated insulin-like growth factor binding protein-1 (pIGFBP-1) test and fetal fibronectin test. Ann Acad Med Singapore 2007;36(6):399-402.
28. Boltovskaia MN, Zaraiskii EI, Fuks BB, Sukhikh GT, Kalafati TI, Starosvetskaia NA, et al. Histochemical and clinical-diagnostic study of placental alpha 1-microglobulin using monoclonal antibodies. Biull Eksp Biol Med 1991;112(10): 397-400. [in Russian]
29. Cousins LM, Smok DP, Lovett SM, Poeltler DM. AmniSure placental alpha macroglobulin-1 rapid immunoassay versus standard diagnostic methods for detection of rupture of membranes. Am J Perinatol 2005;22(6):317-20. doi: 10.1055/s-2005-870896
30. Lee SE, Park JS, Norwitz ER, Kim KW, Park HS, Jun JK. Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes. Obstet Gynecol 2007;109(3):634-40. doi: 10.1097/01.aog.0000252706.46734.0a
31. Ramsauer B, Vidaeff AC, Hösli I, Park JS, Strauss A, Khodjaeva Z, et al. The diagnosis of rupture of fetal membranes (ROM): a meta-analysis. J Perinat Med 2013;41(3):233-40. doi: 10.1515/jpm-2012-0247

Copyright © 2015 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.