Use of Insulin-like Growth Factor Binding Protein-1 for Diagnosis of Ruptured Fetal Membranes in Women With Preterm Labor

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Received 12 April 2006; received in revised form 29 November 2006; accepted 29 November 2006

Abstract

Objective: To evaluate the clinical value of insulin-like growth factor binding protein-1 (IGFBP-1) for detection of rupture of membranes in women with preterm labor and advanced cervical dilatation.
Materials and Method: Seventy-eight women with the diagnosis of preterm labor were evaluated, 44 of whom also had complaints of vaginal fluid leakage. IGFBP-1 level was measured in cervical and vaginal secretions of pregnant women in preterm labor using immunochromatography. Definitive diagnosis of rupture of membranes (ROM) was made using the combination of nitrazine test, amniotic fluid index follow-up, repeated speculum examinations and evaluating the presence of vaginal infections.
Results: Thirty-four women (43%) had the diagnosis of ROM. A positive IGFBP-1 test was detected in 30 (88.2%) women with ROM and 8 (18.2%) women without ROM. The sensitivity of IGFBP-1 detection for the diagnosis of ROM as a single step test in the presence of preterm labor and advanced cervical dilatation was 88% while the specificity was 81%, positive predictive value was 79% and negative predictive value was 90%.
Discussion: IGFBP-1 detection in cervical and vaginal secretions is a valuable single step test in the diagnosis of ruptured membranes even in cases with preterm labor and dilated cervices. It can be used as an adjunct to clinical examination.

Keywords: IGFBP-1, preterm labor, rupture of membranes, diagnosis

Özet

Preterm Doğumda Fetal Membran Rüptürünün Tanısında İnsülin Benzeri Büyüme Faktörü-1 Kullanımı

Amaç: Preterm eylemde olan ve ileri derecede servikal açıklığı olan gebelerde membran rüptürü varlığının tanısında insülin benzeri büyüme faktörü bağlayıcı protein-1'in (IGFBP-1) klinik değerini araştırmak.
Materyal ve Metot: Kırk dördünde (%57) vajinal sıvı akışı şikâyeti de bulunan, preterm eylemdeki 78 gebe değerlendirildi. Preterm eylemdeki tüm kadınların servikal ve vajinal salgılarında immünokromatografik metot ile IGFBP-1 varlığı araştırıldı. Membran rüptürünün kesin tanısı için nitrazin testi, amniotik sıvı endeksi izlemi, tekrarlayan spekulum ölçümleri ve vajinal enfeksiyon varlığı araştırılarak birlikte değerlendirildi.
Sonuç: Otuz dört (%43) hastaya membran rüptürü tanısı konuldu. IGFBP-1 testi membran rüptürü olan 30 kadında (%88.2), olmayan 8 (%18.2) kadında pozitif bulundu. Preterm eylemdeki ileri servikal açıklığı olan kadınlarda, membran rüptürü tanısında IGFBP-1 varlığının araştırılmasına dayanan tek basamaklı testin duyarlılığı %88, özgünlüğü %81, pozitif öngörme değeri %79 ve negatif öngörme değeri %90 bulundu.
Tartışma: Servikal ve vajinal salgılarda IGFBP-1 varlığının araştırılmasına dayanan tek basamaklı test, ileri servikal açıklığı olan preterm eylemdeki olgularda bile membran rüptürü varlığının araştırılmasında değerlidir. Klinik muayeneye yardımcı bir test olarak kullanılabilir.

Anahtar sözcükler: IGFBP-1, preterm doğum eylemi, membran rüptürü, tanı

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Introduction

Premature rupture of membranes (PROM) is defined as observation of amniotic fluid leakage or escape from the cervical canal without any uterine contractions. PROM is not always detected on speculum examination, as there may be no fluid in the vagina despite the patients' complaint of vaginal leakage.

Preterm premature rupture of membranes (PPROM) which complicates 30-50% of all preterm deliveries is a significant cause for maternal and fetal morbidity and mortality (1). Obstetricians and gynecologists need a definitive diagnosis in order to decide on delivering a preterm fetus to prevent intrauterine infection or apply tocolytics to delay delivery in the presence of intact membranes with or without antibiotics. Nitrazine test, fibronectin, IGFBP-1 (insulin-like growth factor binding protein-1) and amniotic fluid measurements were used as screening markers of PPROM diagnosis in different patient populations with variable sensitivity and specificity (2-4).

These available screening tests have low sensitivity and specificity for PPROM diagnosis because same markers also increase in the cervicovaginal secretions due to preterm labor. Several recent studies identified IGFBP-1 as a highly sensitive and specific marker of PROM in term and preterm women (4-6). On the other hand IGFBP-1 was also found to be increased in women with preterm labor in the absence of PROM (7-9). However studies conducted until today had investigated clinical patient populations with suspected preterm premature rupture of membranes while excluding women with preterm labor (4,6) or women with preterm regular contractions while excluding women with PPROM (7-9).

The clinical value of IGFBP-1 detection in cervicovaginal secretions of women with preterm labor and suspected rupture of membranes (ROM) has not been addressed adequately. In this study we have aimed to investigate the value of IGFBP-1 detection in cervicovaginal secretions for the diagnosis of ROM in women with regular uterine contractions accompanied by cervical effacement and dilatation >2 cm.

Materials and Methods

This study was conducted at the TCSB Ankara Etlik Maternity and Women's Health Training and Research Hospital between January and December 2002 and approved by the local ethics commitee. One hundred and twelve consecutive pregnant women with preterm labor defined as regular uterine contractions ≥40 mmHg in amplitude and ≥3 contractions in ten minutes for twenty minutes were evaluated. Seventy-eight women with true preterm labor diagnosed with the presence of cervical effacement exceeding 60% and more than 2 cm dilatation were included in the study.

Exclusion criteria were fetal death, multiple pregnancies, known fetal anomalies, placental problems that may cause oligohydramnios including intrauterine growth restriction and preeclampsia, and diabetes mellitus. Women with active vaginal bleeding and suspected placental abruption were also excluded. We have aimed to perform the study on pregnant women who were diagnosed to have preterm labor and might have benefited from steroid application and aggressive tocolysis for postponing delivery for 48 hours. Those cases with apparent indications for immediate delivery which might have effected the vaginal IGFBP concentrations like vaginal bleeding and diabetes mellitus were excluded from the study (10,11).

After obtaining an informed consent, all women were evaluated with amniotic fluid index measurement, followed by the rapid strip test of amniotic fluid IGFBP-1 (Actim PROM test®, Medix Biochemica, Kauniainen, Finland) in the cervicovaginal secretion, nitrazine test, wet mounts and cultures for vaginal infection, vaginal pH, Bishop score and cervical length measurement. Among the 78 women with preterm labor, forty-four of the pregnant women also had complaints of vaginal fluid leakage.

At the time of admission amniotic fluid index (AFI) was assessed in four quadrants, according to the method of Phelan et al. (12). Sterile speculum examination of the vagina was performed in order to identify amniotic fluid leakage through the cervix. The actim PROM test® is based on the use of two monoclonal antibodies to human IGFBP-1 and immunochromotography. One blue line on dipstick confirms that the test has been performed correctly and there is no IGFBP-1 in the vaginal fluid. Two blue lines on the dipstick indicate that the sample contains IGFBP-1 above 25 µg/L and the test is positive for membrane rupture. Vaginal cultures were obtained from every pregnant woman, vaginal pH was assessed with nitrazine test and Bishop scores were estimated with digital examination of the cervix. Transvaginal ultrasonographic measurements of the cervix were made with a standard technique, as previously described by Iams et al. (13). The flow chart of the definitive diagnosis of ROM is presented in Figure 1 and Figure 2.

Two doses of betametazone 12 mg were given to pregnant women for fetal lung maturation between 24 gestational age and 36 gestational age and repeated 24 hours after the initial dose. Antibiotic prophylaxis using amoxicilin 1g t.i.d. was commenced in every suspected case until definitive diagnosis or all cases with ROM. After exclusion of chorioamnionitis tocolysis was started with ritodrine, MgSO4 or nifedipine on the discretion of attending physician. Twenty-four hours following the second dose of betametazone in ROM cases tocolysis was stopped and labor induction was started.

Statistical analysis of the data was performed using SPSS 11.0. χ^2 and independent samples *t*-tests were used whenever appropriate. The difference was considered to be significant if probability was less than 0.05.

Results

ROM was diagnosed in 34 (43%) of the women in preterm labor while the remaining 44 women constituted the control

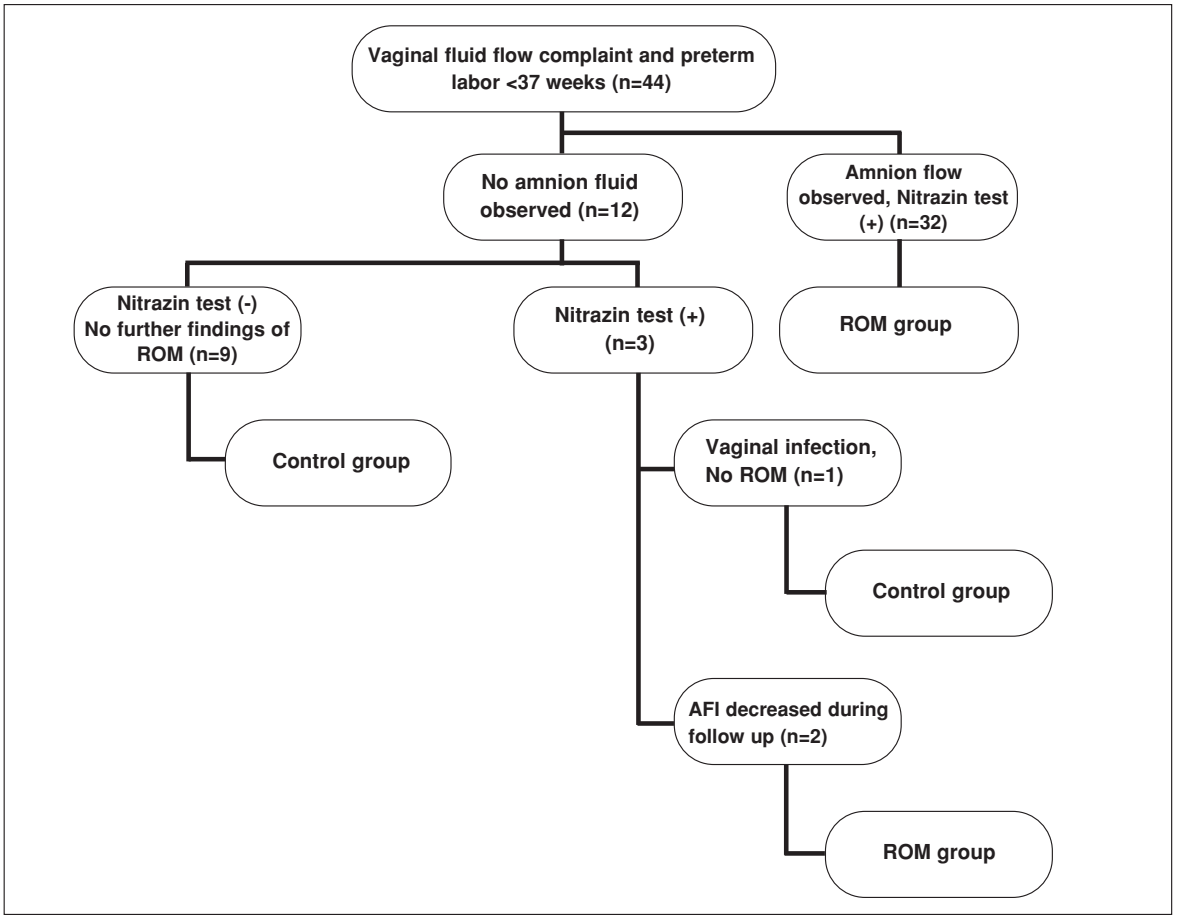

Figure 1. Diagnosis of rupture of the membranes and grouping the women admitted with complaints of vaginal fluid flow and preterm labor

group. Demographic variables of the women were assessed, no difference was found between the ROM group and the control group (Table 1). Mean maternal age, family income, gestational age, frequency of nulliparity, anemia and tobacco use was similar in the two groups.

Presence of the selected variables at the initial examination is shown in Table 2. Ten (22%) women in the control group had the complaint of vaginal fluid flow, which was confirmed not to be ROM with further clinical evaluation and tests. As expected, nitrazine test and IGFBP-1 test were more frequently positive in the ROM group. The mean Bishop score was significantly higher while the mean cervical length was significantly shorter in the ROM group. Urinary tract infection frequency was similar in the two groups.

Table 1. Demographic variables of the women with respect to presence of preterm premature rupture of the membranes

Variable	ROM (n=34)	Control (n=44)	*p*
Maternal age (years)	26.2±5.5	24.1±5	0.08
Income (YTL)	281±94	273±75	0.6
Gestational age (week)	34.3±1.4	33.9±1.8	0.2
Nulliparity	25 (73.5)	30 (68.2)	0.6
Anemia (Hb<10.5)	15 (44.1)	20 (45.5)	0.9
Tobacco use	4 (11.7)	9 (20.4)	0.3

Table 2. Selected variables at the initial examination

Variable	ROM (n=34)	Control (n=44)	*p*
Complaint of vaginal fluid flow	34 (100)	10 (22.7)	<0.001
Bishop Score	4.5±1.4	3.1±1.7	<0.001
IGFBP-1 test positive	30 (88.2)	8 (18.2)	<0.001
Nitrazine test positive	34 (100)	4 (9.0)	<0.001
Cervical length (mm)	22.3±9.5	29.5±13.6	0.01
Fluid pooling observed	32 (94.1)	-	<0.001
Urinary tract infection	7 (20.6)	11 (25)	0.6
Admission to delivery time (hours)	5.6±4.3	24.3±26.9	<0.001

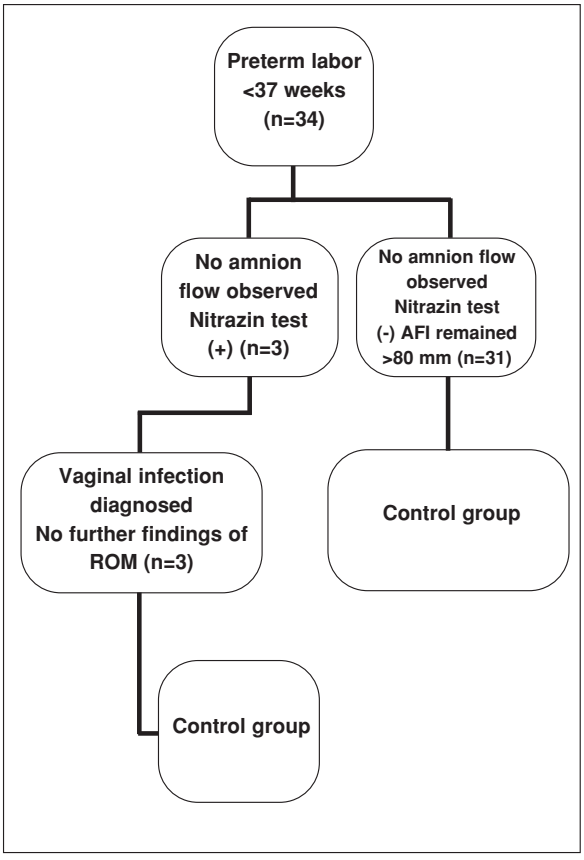

Figure 2. Diagnosis of rupture of the membranes and grouping the women admitted with complaints of preterm labor without vaginal fluid flow

The sensitivity of IGFBP-1 test for detection of ROM was 88%, specificity was 81%, positive predictive value was 79%, and negative predictive value was 90% in the presented study setting. IGFBP-1 test was positive in the two cases without complaints of amniotic fluid leakage but found to have ROM during follow-up (Figure 1).

Discussion

In this study we have evaluated the clinical value of a single step test detecting IGFBP-1 for the diagnosis of ruptured membranes in the presence of advanced cervical dilatation and preterm labor.

IGFBP-1 is an insulin-like growth factor binding protein, which regulates cellular growth and metabolism (14). Insulin-like growth factor binding protein is secreted from human liver, decidual cells and placenta. Its concentrations in the amniotic fluid are 100-1000 fold higher than in serum (15). Detection of IGFBP-1 in the cervical and vaginal secretions has been shown to be a reliable method in the diagnosis of ruptured membranes (4,16).

Unlike nitrazine test or fibronectin tests vaginal infections, discharge, medications, urine or seminal fluids were found to have no effect on the performance of IGFBP-1 test (5). On the other hand, presence of heavy vaginal bleeding may give a positive result due to IGFBP-1 in blood (17). In addition to this, cessation of amniotic fluid leakage for more than 12 h before specimen collection may give a false negative result as IGFBP-1 is degraded by vaginal proteases (5).

IGFBP-1 level increases in the cervical and vaginal secretions of women with threatened preterm labor and ripened cervices even in the absence of ruptured membranes due to membrane stretching and amnion-decidual disruption (5,7,8). Studies conducted in the literature have not specifically addressed the diagnostic accuracy of IGFBP-1 detection in the presence of advanced cervical dilatation and preterm labor. The delivery of 21% of women with advanced cervical dilatation of 3 cm or more may be postponed for a week (18). It is of utmost importance to decrease the possible infectious morbidity in cases with advanced cervical dilatation and ruptured membranes via prophylactic antibiotic use or prompt delivery after corticosteroid injections for fetal lung maturity. Definitive diagnosis of ruptured membranes is essential in the decision-making. In our study we have found that using IGFBP-1 test gives an acceptably high predictive value in the diagnosis of ROM even in dilated and ripened cervices with concomitant uterine contractions.

One of the limitations of our study is that there is no gold standard test utilized like indigo carmine injection. Instead a combination of nitrazine test, speculum examination, amniotic fluid measurement and diagnosing for vaginal infection was utilized. Also, our results should be interpreted with caution, as using IGFBP-1 test alone will miss 12% of ruptured membranes, as the sensitivity is 88% in the presented study setting. As withholding antibiotic use solely due to a negative test might put some fetuses at risk of undiagnosed intrauterine infections, a negative IGFBP-1 test should not lead to decrease in the utility of follow-up tests, such as C-reactive protein, white blood cells or IL-6 levels, for intraamniotic infections.

As a result we would like to conclude that IGFBP-1 detection is a single step test in the diagnosis of ruptured membranes even in cases with preterm labor and dilated cervices. It can be used as a complimentary test in the management algorithm of preterm labors with advanced cervical dilatations.

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