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Insulin-like growth factor binding protein-1 (Actim PROM test®) for detection of premature rupture of fetal membranes

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ABSTRACT

Objective: To detect the accuracy of the IGFBP-1 in diagnosing premature rupture of fetal membranes. **Methods:** One hundred and fifty pregnant women after 37 weeks gestation were included in this study and divided into two groups according to presence or absence of PROM; 75 patients with PROM were included in group I and 75 patients without PROM were included in group II as controls. The diagnosis of PROM was based on patient's history of sudden gush of water, pooling of amniotic fluid, positive Ferning pattern, positive Nitrazine test, confirmed by visualization of fluid passing from the cervical canal during sterile speculum examination and Trans-abdominal ultrasound to measure the amniotic fluid index. **Results:** In this study, the sensitivity and the specificity of IGFBP-1 (Actim PROM test®) in diagnosing PROM were 89.3% & 82.7%, respectively, as compared with 84% sensitivity & 78.7% specificity for Ferning test, and 86.7% sensitivity & 81.3% specificity for Nitrazine test. The PPV and NPV of IGFBP-1 (Actim PROM test®) were 83.8% & 88.6%, respectively, as compared with 79.7% PPV & 83.1% NPV for Ferning test, and 82.2% PPV & 85.9% NPV for Nitrazine test. The IGFBP-1 (Actim PROM test®) was more accurate (86%) for detection of PROM than Ferning (81.3%) or Nitrazine (84.0%) tests. **Conclusion:** The Actim PROM test®, for detection of IGFBP-1 in the vaginal fluid is a simple bedside test, and can be used as complimentary test to confirm the clinical diagnosis of Premature rupture of fetal membranes.

1. Introduction

Premature rupture of membranes (PROM) is rupture of the fetal membranes before the onset of labor and approximately 8%-10% of term pregnancies will experience PROM prior to the onset of uterine activity[1] while rupture of fetal membranes before 37 weeks gestation, is defined as preterm premature rupture of membranes (PPROM)[2]. PROM is usually associated with significant perinatal and maternal infectious morbidities[3]. During the management of patients with PROM the clinician weighs the risk of prolonging gestation against the risks of serious fetal and maternal consequences[4,5]. Failure to identify patients with PROM can result in failure to implement standard measures and conversely an incorrect diagnosis leads to inappropriate interventions (such as hospitalization or induction of labor). Therefore, the diagnosis of PROM is of critical importance to avoid serious fetal or maternal consequences[4]. Accurate diagnosis of PROM remains a frequent clinical problem in obstetrics. Unfortunately, a non-invasive standard diagnostic test is not available at this time and the currently available tests are inaccurate. The diagnosis of PROM is usually based on the patient's history, identification of gross pooling of amniotic fluids from the cervical canal during sterile speculum examination, Ferning pattern after microscopic examination and the Nitrazine test[6,7]. Ferning has been associated with false-positive results in 5%-30%; and false-negative results in 5%-12.9%[7]. Nitrazine evaluation has been associated with false-positive results in 17.4% and false negative results in 12.9%[7]. The absence of a non-invasive gold standard for the diagnosis of rupture of fetal membranes resulted in the appearance of several tests based on alternative biochemical markers. These biochemical markers include vaginal prolactin, alpha feto protein (AFP), fetal fibronectin and insulin like growth factor binding protein 1 (IGFBP 1)[8-10]. However, prolactin & AFP were not useful markers for PROM because of the overlap in concentrations between women with and without ruptured membranes[9]. The human chorionic gonadotropin (HCG) has been evaluated as a marker for PROM, unfortunately, the quantitative evaluation of HCG as a marker for PROM is costly and time consuming[11-13]. Several recent studies suggested that the detection of IGBP-1 in the vaginal fluid will provide qualitative results that will

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exceed the current diagnostic methods in sensitivity and specificity[14-16]. So, this study was designed to detect the accuracy of the IGFBP-1 using Actim PROM test® in diagnosing premature rupture of fetal membranes.

2. Materials and methods

This comparative prospective study was carried out over one year in Ahmadi Hospital, Kuwait Oil Company, from February 2011 till February 2012. One hundred and fifty (150) pregnant women after 37 weeks gestation were included in this study for induction of labor after informed consent and approval of the study protocol by the institute ethical committee and divided into two groups according to presence or absence of PROM; 75 patients with PROM were included in group I and 75 patients without PROM were included in group II for induction of labor due to hypertension or diabetes with pregnancy or IUGR as controls. Patients with multiple pregnancies or fetal distress or vaginal bleeding or preterm labor or chorioamnionitis were excluded from this study.

The diagnosis of PROM was based on patient's history of sudden gush of water, pooling of amniotic fluid, positive Ferning pattern, positive Nitrazine test, confirmed by visualization of fluid passing from the cervical canal during sterile speculum examination and Trans-abdominal ultrasound to measure the amniotic fluid index (AFI $\leqslant$ 5 cm in PROM)[10, 17, 18].

The gestational age was calculate from the first day of LMP and confirmed by early ultrasound scan (done before 20 weeks gestation).

2.1. Methods

Patients included in this study were subjected to standard examination, trans-abdominal ultrasound and sterile speculum examination to detect amniotic fluid pooling through the cervical canal and for collection of samples on admission. Some laboratory investigations were done to exclude chorioamnionitis (maternal fever, maternal tackycardia, fetal tackycardia, maternal leucocytosis, CRP). Samples collection: patients were examined in dorsal Lithotomy position with good illumination using sterile speculum (without antiseptics). Three sterile swabs were used to collect the samples from the posterior vaginal fornix after insertion of the speculum (the swabs should not touch the vaginal wall during insertion or during removal).

2.2. Nitrazine test

the first sterile swab impregnated with nitrazine yellow dye was inserted in the posterior vaginal fornix for 15 seconds and then the colour of the swab was interpreted after removal of the swab from the vagina. The blue colour was considered as positive (PROM) and other colours were considered as negative (no PROM).

2.3. Ferning test

the sample collected from the posterior vaginal fornix using the second swab was spreaded on a glass slide, creating a very thin smear and the smear was examined by low power microscope, crystallization of amniotic fluid to form a fern like pattern was considered as positive (PROM).

2.4. Insulin-like Growth Factor Binding Protein-1 (Actim PROM test®)

According to the manufacturer's instructions, the third Polyester swab provided with the kit was inserted into the vagina for 10-15 seconds, then rinsed in the provided specimen extraction solution or buffer for 10 seconds, then removed from the solution and disposed. The yellow area of the dipstick was dipped into the specimen extraction solution, removed when the liquid reaches the result window and result interpreted as soon as it was visible. If only one blue line was visible, the test result was negative (no PROM), if two blue lines were visible, the test result was positive (PROM) and if no lines were visible, it indicates that the test was not functioning properly or invalid test. One blue line on dipstick confirms that the test has been performed correctly and there is no IGFBP-1 in the vaginal fluid (no PROM). Two blue lines on the dipstick indicate that the sample contains IGFBP-1 (above 25 μg/L), and the test is positive for premature membrane rupture (PROM).

After delivery the collected data on admission were confirmed, reviewed and statistically analyzed to assess the sensitivity, specificity, PPV, NPV and accuracy for each test.

2.5. Statistical analysis

Data were collected, tabulated then statistically analyzed using Statistical Package for Social Sciences (SPSS); computer software version [15]. Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number and percentage. Chi-square test was used for comparison between groups as regard qualitative variables. A difference with P value <0.05 was considered statistically significant, otherwise it was insignificant.

Sensitivity is the proportional detection of individuals with the disease of interest in the population. Specificity: is the proportional detection of individuals without the disease of interest in the population. PPV: is the proportion of all individuals with positive tests, who have the disease. NPV: is the proportion of all individuals with negative tests, who are non-diseased.

3. Results

In this study, there was no significant difference between two studied groups regarding the mean age, which was (31.50 ± 9.52) years in group I (PROM) and (29.10 ± 4.34) years in group II (control group), also, there was no significant difference between the two studied groups regarding the mean gestational age, which was (37.20 ± 8.33) weeks for the group I (PROM), while it was (37.90 ± 2.86) weeks for the group II (control group), (Table 1).

In group I (PROM); the IGFBP-1 (Actim PROM test®) was true positive in 67 patients (89.3% = sensitivity) and it was false negative in 8 patients (10.7%), while in group II (controls); the IGFBP-1 was true negative in 62 patients (82.7% = specificity) and it was false positive in 13 patients (17.3%) (Table 2).

In group I (PROM); the Ferning test was true positive in 63 patients (84.0% = sensitivity) and it was false negative in 12 patients (16.0%), while in group II (controls); the Ferning test was true negative in 59 patients (78.7% = specificity) and it was false positive in 16 patients (21.3%) (Table 2).

In group I (PROM); the Nitrazine test was true positive in 65 patients (86.7% = sensitivity) and it was false negative in 10 patients (13.3%), while in group II (controls); the Nitrazine test was true negative in 61 patients (81.3% = specificity) and it was false positive in 14 patients (18.7%) (Table 2).

The sensitivity & the specificity of IGFBP-1 (Actim PROM test®) in diagnosing PROM were 89.3% & 82.7%, respectively, as compared with 84% sensitivity & 78.7% specificity for Ferning test and 86.7% sensitivity & 81.3% specificity for Nitrazine test (Table 3). The PPV & NPV of IGFBP-1 (Actim PROM test®) were 83.8% & 88.6%, respectively, as compared with 79.7% PPV & 83.1% NPV for Ferning test and 82.2% PPV & 85.9% NPV for Nitrazine test (Table 3). IGFBP-1 (Actim PROM test®) was more accurate (86%) for detection of PROM than Ferning (81.3%) or Nitrazine (84.0%) tests (Table 3).

Table 1

The maternal age and gestational age for the two studied groups.

Variables	Group I (PROM Group = 75)	Group II (Control Group = 75)	*P* value	Significance
Maternal age (years) Mean ± SD	31.5 ± 9.52	29.1 ± 4.34	*P*>0.05	Non-significant
Gestational age (weeks) Mean ± SD	37.2 ± 8.33	37.9 ± 2.86	*P*>0.05	Non-significant

PROM = Premature rupture of membranes.

Table 2

The IGFBP-1 (Actim PROM), Ferning and Nitrazine positive & negative cases in the two studied groups (*n*, %).

Test	Group I (PROM = 75 patients)		Group II (Controls = 75 patients)	
	Positive true (%)	Negative false (%)	Positive false (%)	Negative (%)
IGFBP-1 (Actim PROM test®)	67 (89.3%)	8 (10.7%)	13 (17.3%)	62 (82.7%)
Ferning test	63 (84.0%)	12 (16.0%)	16 (21.3%)	59 (78.7%)
Nitrazine test	65 (86.7%)	10 (13.3%)	14 (18.7%)	61 (81.3%)

IGFBP-1 = Insulin-like Growth Factor Binding Protein-1, PROM = Premature rupture of membranes.

Table 3

The sensitivity, specificity, PPV, NPV, accuracy of IGFBP-1 (Actim PROM), Ferning & Nitrazine tests in diagnosis PROM.

Variables	IGFBP-1 test	Ferning test	Nitrazine test
Sensitivity	67/(67+8) × 100 =89.3 %	63/(63+12) × 100 =84.0%	65/(65+10) × 100 =86.7%
Specificity	62/(62+13) × 100 =82.7 %	59/(59+16) × 100 =78.7%	61/(61+14) × 100 =81.3%
Positive Predicative Value (PPV)	67/(67+13) × 100 =83.8 %	63/(63+16) × 100 =79.7%	65/(65+14) × 100 = 82.2%
Negative Predictive Value (NPV)	62/(62+8) × 100 =88.6%	59/(59+12) × 100 =83.1%	61/(61+10) × 100 =85.9%
Accuracy	67+62/(67+62+13+8) × 100 = 86%	63+59/(63+59+16+12) × 100 = 81.3%	65+61/ (65+61+14+10) × 100 = 84.0 %

IGFBP-1 = Insulin-like Growth Factor Binding Protein-1, PROM = Premature rupture of membranes.
Accuracy = True positive + true negative /(True positive + true negative + false positive + false negative) × 100; IGFBP-1 = Insulin-like Growth Factor Binding Protein-1; Negative Predictive Value (NPV) = True negative /(True negative + false negative) × 100; Positive Predicative Value (PPV) = True positive /(True positive + false positive) × 100; PROM = Premature rupture of membranes; Sensitivity = True positive /(True positive + false negative) × 100; Specificity =True negative /(True negative + false positive) × 100

4. Discussion

PROM is usually associated with significant perinatal and maternal infectious morbidities[19]. Ferning has been associated with false-positive results in 5%-30%; due to contamination with fingerprints on a slide or contamination with semen or cervical mucus and false-negative results in 5%-12.9%; due to dry swabs or contamination with blood[5,7]. Nitrazine evaluation has been associated with false-positive results in 17.4%; due to cervicitis, vaginitis, alkaline urine, blood, semen or antiseptics and false negative results in 12.9%[5,7].

Detection of IGFBP-1 in the vaginal fluid using Actim PROM test® is a one-step bed side test, which provides qualitative results that will exceed the current diagnostic methods in sensitivity and specificity[14-16]. So, this study was designed to detect the accuracy of IGFBP-1 (Actim PROM test®) in diagnosing premature rupture of fetal membranes.

IGFBP-1 is an insulin-like growth factor binding protein, which regulates cellular growth and metabolism.[20] 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[5]. The Actim PROM test® is immunochromatography test based on the use of two monoclonal antibodies to human IGFBP-1 and give positive result for PROM when the sample contains IGFBP-1 above 25 μg/L. 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 presence of IGFBP-1 in the blood[5].

In this study; the IGFBP-1 (Actim PROM test®) was more sensitive & specific in diagnosing rupture of fetal membranes than Ferning or Nitrazine tests, the sensitivity & the specificity of IGFBP-1 (Actim PROM test®) in diagnosing PROM were 89.3% & 82.7%, respectively, as compared with 84% sensitivity & 78.7% specificity for Ferning test and 86.7% sensitivity & 81.3% specificity for Nitrazine test. The PPV & NPV of IGFBP-1 (Actim PROM test®) were 83.8% & 88.6%, respectively, as compared with 79.7% PPV & 83.1% NPV for Ferning test and 82.2% PPV & 85.9% NPV for Nitrazine test. IGFBP-1 (Actim PROM test®) was more accurate (86%) for detection of PROM than Ferning (81.3%) or Nitrazine (84.0%) tests.

Seventy-eight (78) women with the diagnosis of preterm labor (44 of them had definite ROM), were included in Dilbaz & colleagues study, to detect the clinical value of IGFBP-1 for detection of rupture of membranes in women with preterm labor[5]. Dilbaz & colleagues found the sensitivity of the dipstick test for IGFBP-1 in detection of ROM was 88%, while the specificity was 81%, PPV was 79% and NPV was 90%. They concluded that the dip stick test for IGFBP-1 is a valuable single step test in the diagnosis of ROM even in cases with preterm labor and it can be used as an adjunct to confirm clinical diagnosis[5].

Also, One hundred and fifty-one (151) patients (36 definite PROM, 35 no PROM and 80 suspected PROM) at 20-42 weeks' gestation were included in Erdemoglu *et al* study, which was designed to compare the accuracy of the IGFBP-1 dipstick test with the accuracy of the Nitrazine test in diagnosing PROM. Erdemoglu and colleagues found, that the Actim PROM test® had the same sensitivity (97%) like Nitrazine test, but more specific (97% versus 16%), and more accurate (97% versus 56%) than Nitrazine test in detection of PROM[14]. Erdemoglu and colleagues, concluded that the Actim PROM test® is a rapid, reliable, non-invasive and accurate method to confirm the amniotic fluid leakage in patients with suspected PROM, also, they concluded that unlike Nitrazine test, Actim PROM test® was not affected by the vaginal discharge[14].

Cessation of amniotic fluid leakage for more than 12 hours before specimen collection may give a false negative result as IGFBP-1 is degraded by vaginal proteases. 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[21, 22]. This explains, why in this study, the Actim PROM test® gave false negative result in 8 (10.7%) cases of definite PROM and false positive result in 13 (17.3%) cases without PROM. This failure to identify patients with PROM can result in failure to implement standard measures such as hospitalization or antibiotics therapy.

One hundred and seventy-four (174) women were included in a multicenter study, which was designed to investigate whether IGFBP-1 dipstick test could confirm or exclude amniotic fluid leakage by Darj *et al*.[23] Darj *et al*, found that the Actim PROM test® had 95.7% sensitivity, 93.1% specificity for cases with definite PROM and had less sensitivity (70.8%), less specificity (88.2%) and 92% PPV for cases with suspected PROM[23]. Darj and colleagues, concluded that the Actim PROM test® with monoclonal antibodies to IGFBP-1 had high PPV, high sensitivity and specificity and it is useful to be used as complimentary test to confirm the clinical diagnosis of PROM, but patients with a negative test should be followed up by C-reactive protein and white blood cells, to avoid intra-amniotic infections[23].

The clinical usefulness of IGFBP-1 dipstick test in the detection of ROM was evaluated by Rutanen and colleagues[24]. Cervicovaginal secretion was sampled between 15 and 37 weeks of gestation from women with intact membranes and from women with clinically confirmed ROM, as well as from women with suspected ROM based on history, they concluded that a positive Actim PROM test® result identifies ruptured fetal membranes with high sensitivity and a negative test result effectively excludes those with intact membranes[24].

The performance of two rapid tests for the diagnosis of PROM based on the detection of the insulin-like growth factor-binding protein-1 (IGFBP-1) and placental Alpha-microglobulin-1 (PAMG-1) in cervicovaginal secretions were compared by Marcellin and coleagues[25] .They found that, the AmniSure (PAMG-1) test was 95% sensitive, 94.8% specific, with 95% PPV and 94.8% NPV in diagnosing PROM, while the Actim PROM (IGFBP-1) test was 97.5% sensitive, 97.4% specific, with 97.5 % PPV and 97.4 % NPV in diagnosing PROM. Marcellin and colleagues concluded that both AmniSure (PAMG-1) and Actim PROM (IGFBP-1) tests have similar performance to diagnose premature rupture of membranes[25]. Also, the diagnostic efficacy of PAMG-1 and IGFBP-1 tests in PROM were evaluated by Albayrak et al, and they concluded that both rapid bedside strip tests may be used in clinical practice with similar efficacy in diagnosing PROM, particularly as a backup when diagnosis is still in doubt following a combination of conventional diagnostic methods[26].

The value of insulin-like growth factor binding protein-1 (IGFBP-1) and other tests for the diagnosis of rupture of the membranes (ROM) were evaluated by Martinez de Tejada *et al*[27]. They found that the IGFBP-1 was 86% sensitive, 74% specific, with 73%PPV and 87% NPV in diagnosing ROM and they concluded that the dipstick test of IGFBP-1 in sensitive bedside test for detection of ROM[27].

. In this study; The Actim PROM test®, for detection of IGFBP-1 in the vaginal fluid was a simple bedside one step test, more sensitive and specific than Ferning and Nitrazine tests, can be used as complimentary test to confirm the clinical diagnosis of Premature rupture of fetal membranes.

Conflict of interest Statement

No actual or potential conflict of interest in relation to this article exists.

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