ORIGINAL ARTICLE

Insulin-like Growth Factor Binding Protein-1/ alpha-fetoprotein versus Placental alpha microglobulin-1 for diagnosis of premature fetal membranes rupture

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Article Information

Received: 22 Sep 2015
Accepted: 10 Nov 2015
Plagiarism software: Turnitin

Keywords:
IGFBP-1,
AFP,
PAMG-1,
PROM

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ABSTRACT

Objectives: To compare insulin-like growth factor binding protein-1/alpha-fetoprotein (IGFBP-1/AFP) to placental alpha microglobulin-1 (PAMG-1) for diagnosis of premature fetal membranes rupture (PROM).

Methods: 220 pregnant women ≥ 37 and < 39 weeks` gestation studied and classified into two groups; study group (PROM) and control group (no PROM). Examination of the studied women followed by abdominal ultrasound (TAS) and sterile vaginal speculum examination to visualize amniotic fluid leaking and for collection of samples for fern, nitrazine, AmniSure® and AmnioQuick® Duo+ tests on admission.

Results: The sensitivity and specificity of AmnioQuick® Duo+ test to detect PROM was 93.6% and 86.4%; respectively compared to 95.5% and 89.1%; respectively for AmniSure® test, 72.7% and 80.9%; respectively for fern test and 76.4% and 83.6%; respectively for nitrazine test. PPV, NPV and accuracy of AmnioQuick® Duo+ test to detect PROM were 87.3%, 93.1% and 90%; respectively compared to 89.7, 95.1% and 92.3%; respectively for AmniSure® test, 79.2%, 74.8% and 76.8%; respectively for fern test and 82.4%, 77.97% and 80%; respectively for nitrazine test. AmnioQuick® Duo+ and AmniSure® tests had higher sensitivity, specificity, predictive values and accuracy to detect PROM compared to conventional diagnostic tests.

Conclusion: AmnioQuick® Duo+ test for detection of IGFBP-1/AFP was rapid, accurate bedside test better than the individual conventional diagnostic tests and has same accuracy and performance like AmniSure® test.

INTRODUCTION

Premature fetal membranes rupture (PROM) is fetal membranes rupture before the onset of labour.[1] Preterm premature fetal membranes rupture (PPROM) is fetal membranes rupture before 37 weeks` gestation.[2]

PROM occurs in 2 -18% of all pregnancies, while, PPROM occurs in 0.7-4%.[3]

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DOI: 10.5530ami.2016.1.15	

Management of ruptured fetal membranes (ROM) should be conservative if ROM occurs before 37 weeks` gestation, while, labour should induced if ROM occurs at term.[4]

Failure to identify women with PROM associated with failure to implement standard measures and infectious morbidities.[1,2,5-7]

ROM is a common problem in obstetrics due to absence of non-invasive standard diagnostic test.[7] The absence of a non-invasive standard test for diagnosis of ROM leads to appearance of several biological tests based on alternative markers that highly present in amniotic fluid.[4]

These markers include; HCG (human chorionic gonadotropin),[8-10] alpha-fetoprotein (AFP), fetal

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fibronectin (fFN),[11] Placental alpha microglobulin-1 (PAMG-1)[7-12] and insulin-like growth factor binding protein-1 (IGFBP-1).[13-18]

Previous studies suggested that PAMG-1 and IGFBP-1 detection in the vaginal fluid would be more accurate in the diagnosis of PROM than the current diagnostic methods.[7,12,14,15]

Recently, a new, rapid immunoassay test (AmnioQuick® Duo+) test can detect two markers (IGFBP-1 and AFP) present in the amniotic fluid.[4]

PATIENTS AND METHODS

This comparative study conducted from July 2013 until July 2014 in Ahmadi Hospital, Kuwait. Two hundred and twenty pregnant women ≥ 37 and < 39 weeks` gestation admitted for induction of labour studied after informed consent and approval of the local ethical committee of Ahmadi Hospital.

Studied women classified into two groups; study group (110 women with PROM) and control group (110 women without PROM) admitted for induction of labour due to intrauterine growth retardation or diabetes or hypertension with pregnancy.

Women with the following excluded from this study; ROM beyond 39 weeks` gestation or prolonged PROM (>12 hours) or non-reassuring fetal cardio-tocography (CTG) or multiple pregnancies or ante-partum hemorrhage or preterm labour or infection of fetal membranes (chorioamnionitis).

The PROM diagnosed by history of gush of amniotic fluid, positive fern and nitrazine tests, confirmed by fluid leaking fluid from the cervix during speculum examination and amniotic fluid index ≤ 5 cm.[7,11]

Gestational age of the studied women calculated accurately from last menstrual period and early scan done before 20 weeks.

Examination of studied women followed by TAS and sterile vaginal speculum examination to detect leaking fluid and for collection of samples for fern, nitrazine, AmniSure® and AmnioQuick® Duo+ tests on admission.

In addition, maternal fever and tackycardia, fetal tackycardia, maternal leucocytosis, C-reactive proteins evaluated for all studied women to exclude chorioamnionitis.[19,20]

Studied women examined in Lithotomy position with proper illumination for samples collection using sterile vaginal speculum.

Four sterile swabs used to collect the samples from the posterior vaginal fornix. The first nitrazine yellow swab inserted for 15 seconds in the posterior vaginal fornix and then the colour of the swab checked.

The sample of the fluid collected from the posterior vaginal fornix using the second swab spreaded on a glass slide, creating a thin smear and examined by low power microscope (fern test).

PAMG-1 (AmniSure® test) done following manufacturer's instructions (QIAGEN, Maryland, USA) using third swab which inserted into the vagina for 1 minute, then rinsed in the solvent for 1 minute, then removed from the solvent and disposed. Test strip dipped into the solvent for 5-10 minutes and the results interpreted.[3,7]

IGFBP-1/AFP (AmnioQuick® Duo+) done following manufacturer's instructions. Fourth Nylon swab supplied in the AmnioQuick® Duo+ (Biosynex, Strasbourg, France) kit package inserted in the posterior fornix of the vagina for 1 minute. Then, the swab removed, inserted into a unit dose vial containing solvent and rotated for 10 seconds into the solvent. Three drops of the extracted substance from the swab by the solvent dispensed into a round sample well of the test device.

The result interpreted in 10 minutes. The test positive when both C and B lines present or when both A and C lines present. The test negative when both A and B lines absent. Test invalid when no visible purple band at line C.[4,21] Figure 1.

A final diagnosis of whether the studied women had PROM or not at the initial presentation made after delivery by blinded investigator to the AmnioQuick® Duo+ and AmniSure results. After delivery, the recorded information of admission and delivery analysed to compare AmnioQuick® Duo+ (IGFBP-1/AFP) to AmniSure (PAMG-1) for diagnosis of PROM.

SAMPLE SIZE JUSTIFICATION

The effective sample size was calculated using G* Power software (*Heinrich Heine Universität; Düsseldorf; Germany) and data of previous studies.[5,7]

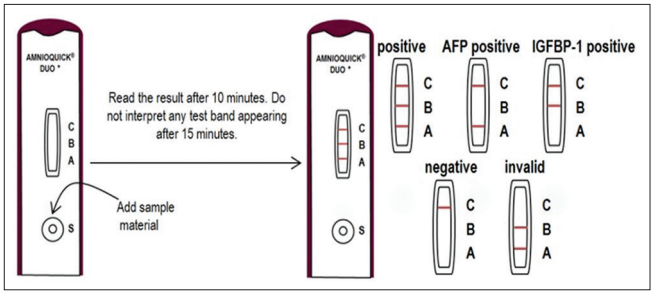

Figure 1: AmniQuick® Duo+ test results

Statistical Analysis

Data analysed using Statistical Package for Social Sciences. Mean and standard deviation (±SD) used to present numerical variables, while number (n) and percentage (%) used to present categorical variables. Qualitative variables analysed using Chi-square (X^2) test and quantitative variables analysed using Student t test. p value <0.05 considered significant. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of used tests were also calculated.

RESULTS

There was no significant difference between study (PROM) and control group (no PROM) regarding; mean maternal age and gestational age.

AmnioQuick® Duo⁺ test was true positive (TP) in 103 women (93.6% sensitivity) and false negative (FN) in 7 women (6.4%) of the study group, while it was true negative (TN) in 95 women (86.4% specificity) and false positive (FP) in 15 women (13.6%) of the control group.

AmniSure® test was TP in 105 women (95.5% = sensitivity) and FN in 5 women (4.5%) of the study group, while it was TN in 98 women (89.1% = specificity) and FP in 12 women (10.9%) of the control group.

Fern test was TP in 80 women (72.7% sensitivity) and FN in 30 women (27.3%) of the study group; while it was TN in 89 women (80.9% specificity) and FP in 21 women (19.1%) of the control group.

Nitrazine test was TP in 84 women (76.4% sensitivity) and FN in 26 women (23.6%) of the study group; while it was TN in 92 women (83.6% specificity) and FP in 18 women (16.4%) of the control group. Table 1

Sensitivity and specificity of AmnioQuick® Duo⁺ test to detect PROM was 93.6% and 86.4%; respectively compared to 95.5% and 89.1%; respectively for AmniSure® test, 72.7% and 80.9%; respectively for fern test and 76.4% and 83.6%; respectively for nitrazine test.

PPV, NPV and accuracy of AmnioQuick® Duo⁺ test to detect PROM were 87.3%, 93.1% and 90%; respectively compared with 89.7, 95.1% and 92.3%; respectively for AmniSure® test, 79.2%, 74.8% and 76.8%; respectively for fern test and 82.4%, 77.97% and 80%; respectively for nitrazine test Table 2.

AmnioQuick® Duo⁺ and AmniSure® tests had higher predictive values and accuracy to detect PROM compared to conventional diagnostic tests (fern and nitrazine) and this difference was statistically insignificant Table 3.

Table 1: Results of AmnioQuick® Duo⁺, Amnisure®, fern and nitrazine tests in studied groups

Variables	Number (%)			
	Study group (PROM) Number 110		Control group (no PROM) Number 110	
	True positive cases (TP)	False negative cases (FN)	False positive cases (FP)	True negative cases (TN)
AmnioQuick® Duo test	103 (93.6)	7 (6.4)	15 (13.6)	95 (86.4)
Amnisure® test	105 (95.5)	5 (4.5)	12 (10.9)	98 (89.1)
Fern test	80 (72.7)	30 (27.3)	21 (19.1)	89 (80.9)
Nitrazine test	84 (76.4)	26 (23.6)	18 (16.4)	92 (83.6)

FN: False negative, FP: False positive, TN: True negative, TP: True positive, PROM: Premature rupture of fetal membranes

DISCUSSION

Failure to identify women with PROM is associated with failure to implement standard measures and infectious morbidities.[1,2,5-7]

False positive results are high with conventional diagnostic tests (fern and nitrazine) used to diagnose PROM.[7]

AmniSure® test is an immunoassay test depends on antibodies that detect PAMG-1 present in amniotic fluid and in cervico-vaginal secretion after ROM. The threshold of AmniSure® test for detection of PAMG-1 is 5 ng/ml.[3,7] PAMG-1 used to detect ROM due to high concentration in the amniotic fluid, low concentration in blood and low concentration in cervical secretions when fetal membranes are intact.[3,7]

AmnioQuick® Duo⁺ can detect amniotic fluid in a sample of vaginal secretions through identification of two biochemical markers (IGFBP-1 and AFP) whose concentration in amniotic fluid is very high.[4,21]

IGFBP-1 level in the amniotic fluid are 100-1000 times higher than in the serum. Threshold for IGFBP-1 detection using AmnioQuick® Duo⁺ is 10 ng/ml.[4]

Because the threshold for IGFBP-1 detection using AmnioQuick® Duo⁺ is 10 ng/ml, the PPV of AmnioQuick® Duo⁺ for IGFBP-1 is therefore very high.[4,21]

The concentration of AFP is fluctuating during pregnancy, it significantly decreases during the 3rd trimester of pregnancy and because the threshold of AmnioQuick® Duo⁺ for detection of AFP is 5 ng/ml, the PPV of AmnioQuick® Duo⁺ for AFP is very high beyond 37 weeks` gestational age.[4,21]

Table 2: Predictive values and accuracy of AmnioQuick® Duo⁺, AmniSure®, fern and nitrazine tests to detect PROM in studied groups

Variables	AmnioQuick Duo⁺ test (%)	AmniSure® test (%)	Fern test (%)	Nitrazine test (%)
Sensitivity=TP/(TP+FN)×100	103/(103+7)×100=93.6	105/(105+5)×100=95.5	80/(80+30)×100=72.7	84/(84+26)×100=76.4
Specificity=TN/(TN+FP)×100	95/(95+15)×100=86.4	98/(98+12)×100=89.1	89/(89+21)×100=80.9	92/(92+18)×100=83.6
PPV=TP/(TP+FP)×100	103/(103+15)×100=87.3	105/(105+12)×100=89.7	80/(80+21)×100=79.2	84/(84+18)×100=82.4
NPV=TN/(TN+FN)×100	95/(95+7)×100=93.1	98/(98+5)×100=95.1	89/(89+30)×100=74.8	92/(92+26)×100=77.97
Accuracy=TP+TN/(TP+TN+FP+FN)×100	103+95/(103+95+15+7)×100=90	105+98/(105+98+12+5)×100=92.3	80+89/(80+89+21+30)×100=76.8	84+92/(84+92+18+26)×100=80

FN: False negative, FP: False positive, NPV: Negative predictive value, PPV: Positive predictive value, TN: True negative, TP: True positive

Women with ante-partum hemorrhage excluded from this study because presence of blood in the collected samples can lead to false positive results of AmnioQuick® Duo⁺ test.

In addition, because, prolonged PROM (>12 hours) increases liability of IGFBP-1 and PAMG-1 degradation by vaginal proteases and AFP concentration decreases in amniotic fluid beyond 39 weeks` gestation, women with prolonged PROM and women with PROM beyond 39 weeks` gestation excluded from this study.[4,12,21]

In this study, the AmnioQuick® Duo⁺ test had 93.6% sensitivity, 86.4% specificity, 87.3% PPV, 93.1% NPV and 90% accuracy.

Ruanphoo et al, concluded that; AmnioQuick® Duo⁺ had 94.1% sensitivity, 87.5% specificity, 97.5% PPV, 73.7% NPV and 93% accuarcy.[4]

In addition, Thomasino et al, evaluated the performance of combined monoclonal/polyclonal immunoassay test using placental protein-12 (PP12)/AFP (ROM Plus) to diagnose ROM and they found that the combined PP12/AFP immunoassay had 99% sensitivity, 91% specificity, 95% PPV and 99% NPV.[22]

AmniSure® test in this study had 95.5% sensitivity, 89.1% specificity, 89.7 PPV, 95.1% NPV and 92.3% accuracy to detect PROM.

Cousins et al, found that AmniSure® test had 98.9% sensitivity, 100% specificity, 100% PPV and 99.1% NPV in diagnosing PROM and Lee and colleagues, concluded that AmniSure® test was superior to conventional methods in diagnosing PROM.[23,24]

Gian et al and Birkenmaier et al, concluded that the AmniSure test is reliable and cost effective in diagnosing ROM.[19,25]

In this study, the sensitivity and specificity of AmnioQuick® Duo⁺ and AmniSure® tests to detect PROM were higher than fern and nitrazine tests. In addition, the PPV, NPV and accuracy of AmnioQuick® Duo⁺ and AmniSure® tests to detect PROM were higher than fern and nitrazine tests.

Ruanphoo et al concluded that; the sensitivity of the AmnioQuick® Duo⁺ test was higher than the standard methods in diagnosing ROM, because the AmnioQuick® Duo⁺ test detect two markers in the amniotic fluid at very low threshold (IGFBP-1 at 10 ng/ml and AFP at 5 ng/ml).[4]

Table 3: Predictive values and accuracy of AmnioQuick® Duo⁺ and AmniSure® tests to detect PROM compared to standard diagnostic tests

Variables	AmnioQuick Duo⁺ test (%)	AmniSure® test (%)	Fern test (%)	Nitrazine test (%)	p value, significance
Sensitivity	93.6	95.5	72.7	76.4	p=1 (>0.05), NS *p=0.22 (>0.05), NS **p=0.32 (>0.05), NS
Specificity	86.4	89.1	80.9	83.6	p=0.87 (>0.05), NS *p=0.74 (>0.05), NS **p=0.87 (>0.05), NS
Positive predictive value (PPV)	87.3	89.7	79.2	82.4	p=1 (>0.05), NS *p=0.63 (>0.05), NS **p=0.77 (>0.05), NS
Negative predictive value (NPV)	93.1	95.1	74.8	77.97	p=1 (>0.05), NS *p=0.28 (>0.05), NS **p=0.38 (>0.05), NS
Accuracy	90	92.3	76.8	80	p=1 (>0.05), NS *p=0.44 (>0.05), NS **p=0.56 (>0.05), NS

p value when AmnioQuick® Duo⁺ test compared to AmniSure® test, *P-value when AmnioQuick® Duo⁺ test compared to fern test, **P-value when AmnioQuick® Duo⁺ test compared to nitrazine test Chi-square (X2) used for statistical analysis, NS: Non-significant, PROM: Premature rupture of fetal membranes

Thomasino et al, concluded that the combined immunoassay test using PP12/AFP for detection of ROM was better than the individual components of conventional tests (fern and nitrazine).[22]

Marcellin et al and Albayrak et al, found that both PAMG-1 (AmniSure®) and IGFBP-1 (Actim PROM®) tests has similar efficacy in diagnosing PROM, particularly as a backup when diagnosis is doubtful following conventional methods.[17,18]

In this study, AmnioQuick® Duo⁺ and AmniSure® tests had higher sensitivity, specificity, predictive values and accuracy in detection of PROM compared to conventional tests, but this difference was statistically insignificant (using Chi-square test (X^2); $p > 0.05$).

Ruanphoo et al, in their study mentioned the accuracy of AmnioQuick® Duo⁺ and standard methods in diagnosing ROM, without statistical analysis or comparison between used diagnostic methods.[4,22]

This is first study conducted to evaluate the accuracy of AmnioQuick® Duo⁺ as a new immunoassay test compared with AmniSure® test in detection of PROM. The strength of this study is coming from participants' selection, proper sample size, statistical analysis and comparative nature of the study.

Because AmnioQuick® Duo⁺ test is new, immunoassay test detect two biological markers present in the amniotic fluid, little available data and studies about AmnioQuick® Duo⁺ test was the only limitation faced during this study.

In this study, the AmnioQuick® Duo⁺ test for detection of IGFBP-1/AFP was rapid, accurate bedside immunoassay test better than the individual conventional diagnostic tests and has same accuracy and performance like AmniSure® test.

ACKNOWLEDGEMENT

Authors appreciate the effort done by Doctor Thierry Paper, President of Biosynex SA, for his continuous support and supply of the AmnioQuick® Duo⁺ kits used during this study.

Disclaimer

Biosynex SA, France supplied the AmnioQuick® Duo⁺ kits and not involved in any part of this study or analysis of the data.

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How to cite this article: Abdelazim IA, Al-Sherbeeny MM, Ibrahim MEM, Fahmy AA, Rabei NH, Khalifa AAA. Insulin-like growth factor binding protein-1/ alpha-fetoprotein versus placental alpha microglobulin-1 for diagnosis of premature fetal membranes rupture. Acta Medica International. 2016;3(1):69-74.

Source of Support: Nil, **Conflict of Interest:** None declared.