Diagnostoc Value of IGFBP-1 Rapid Test and Combined IGFBP-1-AFP in Vaginal from Premature Rupture of Amniotic Membranes

by Aryati Aryati

Research Article

Diagnostic Value of IGFBP-1 Rapid Test and Combined IGFBP-1-AFP in Vaginal Fluid from Premature Rupture of Amniotic Membranes

Nilai Diagnostik Insulin-like Growth Factor Binding Protein 1 (IGFBP-1) dan Kombinasi IGFBP-1-alpha-fetoprotein (IGFBP-1-AFP) di Cairan Vagina pada Kejadian Ketuban Pecah Prematur

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Abstract

Objective: To compare the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP rapid tests in diagnosing premature rupture of membranes (PROM).

Method: This study was conducted in Dr. Soetomo Hospital in Surabaya from July to November 2013. The subjects were 52 pregnant women with presumed PROM diagnosis, which was recorded by clinical data and sampling of vaginal discharge swab. The diagnostic value was obtained by comparing the results of IGFBP-1 and combined IGFBP-1-AFP rapid tests by standard PROM examination namely vaginal pooling, litmus paper test and ferning test.

Result: A difference between the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP rapid tests in diagnosing PROM was shown, where the sensitivity and specificity of IGFBP-1 rapid test was 85% and 95%, compared to combined IGFBP-1-AFP rapid test, which was 91% and 95%. The correlation coefficient of combined IGFBP-1-AFP rapid test with standard PROM examination (r=0.841, p=0.000) was higher than the correlation coefficient of IGFBP-1-AFP rapid test with standard PROM examination (r=0.772, p=0.000).

Conclusion: Combined IGFBP-1-AFP rapid test has a better diagnostic value than IGFBP-1 rapid test alone.

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

Abstrak

Tujuan: Mengetahui perbandingan nilai diagnostik rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dalam mendiagnosis KPP.

Metode: Penelitian ini dilakukan di RSUD Dr. Soetomo Surabaya sejak Juli sampai November 2013. Subjek penelitian adalah 52 ibu hamil dengan dugaan diagnosis KPP, dicatat data klinisnya dan dilakukan pengambilan sampel swab cairan vagina. Nilai diagnostik diperoleh dengan membandingkan hasil rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dengan pemeriksaan standar KPP, yaitu vaginal pooling, tes kertas lakmus dan tes ferning.

Hasil: Terdapat perbedaan antara nilai diagnostik rapid test IGFBP-1 dan kombinasi IGFBP-1-AFP dalam mendiagnosis KPP, yaitu sensitivitas dan spesifisitas rapid test IGFBP-1 ditemukan 85% dan 95%, dibandingkan kombinasi IGFBP-1-AFP yaitu 91% dan 95%. Koefisien korelasi rapid test IGFBP-1 dengan pemeriksaan standar KPP (r=0,772, p=0,000) lebih besar dibandingkan koefisien korelasi rapid test kombinasi IGFBP-1-AFP dengan pemeriksaan standar KPP (r=0,841, p=0,000).

Kesimpulan: Rapid test kombinasi IGFBP-1-AFP mempunyai nilai diagnostik yang lebih baik dibandingkan rapid test IGFBP-1 saja.

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Kata kunci: IGFBP-1, kombinasi IGFBP-1-AFP, KPP

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INTRODUCTION

A Prelabor or Premature Rupture of Amniotic Membranes (PROM) is defined as a condition of spontaneous ruptured membranes within 1 hour or more before the onset of labor, as indicated by general symptoms such as a large discharge of vaginal fluid. Differential diagnosis of this condition is excessive urinary incontinence, vaginal mucus for physiological or pathological causes, and cervical mucus during the labor process.[1,2]

The incidence of PROM is relatively high, reaching 10-12% of all pregnancies, making it the major cause of premature childbirth in the United States of America. The leaking of amniotic fluids is also related to increased infection in the mother and baby, which is the the primary cause of infection to both the mother and baby.[3]

PROM diagnosis is always established through anamnesis, clinical examination and vaginal speculum examination. A standard examination for PROM diagnosis is the existence of vaginal pooling in vaginal speculum examination, litmus paper test and ferning body in microscopic examination of vaginal fluid. A small amount of fluid or leakage of vaginal fluid in several cases makes PROM difficult to detect, and the pregnant women rarely realizes it. The pregnant women always fail to differ whether the vaginal discharge is amniotic fluid, urine or mucus. Clinicians have experienced difficulty to establish a diagnosis only based on anamnesis, clinical examination and vaginal speculum examination in as much as 47% of PROM cases.[2,4] The standard examination for detecting leaked amniotic fluid always raised doubt in clinicians regarding establishing the PROM diagnosis, so that many researchers have ventured to find a more objective test.

Amniotic fluid detection may be conducted through immunology testing to detect the molecules existing in high-concentration in the amniotic fluid; such as fibronectin, insulin-like growth factor binding protein-1 (IGFBP-1), alpha-fetoprotein (AFP) and others. This reasearch aims to identify and compare the diagnostic value of IGFBP-1 and combined IGFBP-1-AFP in the amniotic fluid with standard PROM examination, such as vaginal pooling examination using vaginal speculum, vaginal fluid's pH examination using litmus paper test, and ferning body examination with vaginal fluid microscopy for PROM diagnosis.

METHOD

This is an observational-analytic research with a cross-sectional approach. It was conducted at the Department of Clinical Pathology, Faculty of Medicine, Airlangga University, and the delivery room and maternity outpatient clinic of Dr. Soetomo Hospital, Surabaya starting from July to November 2013.

The subjects of this research were pregnant women visiting the delivery room of Dr. Soetomo Hospital, Surabaya with complaints of vaginal fluid discharge who met the criteria of subject acceptance and rejection criteria to conduct amniotic fluid examination using *Amnioquick* (IGFBP-1) and *Amnioquick Plus 2* (combined IGFBP-1-AFP) *rapid tests* until the maximum sample was fulfilled. The inclusion criteria were second and third trimester pregnant women complaining of fluid leakage or discharge. The exclusion criteria was presence of vaginal bleeding. The minimum number of subjects based on sample calculation was 36 patients.

Sampling was conducted during the patients' visit to the delivery room of Dr. Soetomo Hospital. We obtained 52 samples with complaints of vaginal fluid discharge in 5 months starting from July to November 2013.

To perform the assessment, the research subject was placed in the lithotomy position. A sterile and disposable vaginal speculum was then placed in the vagina and presence of vaginal pooling was observed in the posterior fornix. A red litmus paper was contacted with the fluid existing in the posterior fornix; and if the color turned blue, it was evident that it was amniotic fluid. A vaginal sample was taken with a sterile and disposable swab from the posterior fornix area. The vaginal fluid swab was conducted 3 times; the first swab was for *Amnioquick Plus 2 rapid test* examination, the second was for *Amnioquick rapid test* and the third was for a ferning test. The vaginal fluid swab for the *Amnioquick rapid test* and *Amnioquick Plus 2* examinations was kept for about 1 minute. The examination to observe the existence of ferning body was conducted by dropping vaginal secretion or spreading vaginal fluid on an object glass which was kept until dry. The microscopy examination was performed using a microscope with 100x magnification, which would display fern pattern showing the indication of amniotic fluid and PROM.

The examinations with *Amnioquick* and *Amnioquick Plus 2 rapid tests* were conducted by dipping a vaginal fluid swab in a buffer solution for about 10 seconds. The test strip was put in the buffer solution with arrow mark at strip test directed to the bottom and the strip touching the bottom of the buffer solution vial. The test strip was kept for about 10 minutes in the buffer solution. The result of *Amnioquick* and *Amnioquick Plus 2 rapid tests* may be interpreted after the 10 minutes. The appearance of a purple/pink control line on the test strip showed that the procedure was conducted correctly. The test result was not allowed to be interpreted after more than 15 minutes after the test strip was in the buffer solution. The *Amnioquick Plus 2* examination was conducted almost at the same time with *Amnioquick* examination. The interpretation result of *Amnioquick Plus 2* showed 3 categories, which were positive, negative and doubtful. For the interest of analysis, the interpretation of *Amnio-*

quick Plus 2 was changed to 2 categories, namely positive and negative. There were 3 subjects showing a doubtful result. The three research subjects were then observed further into the labor period, and based on diagnosis upon leaving the hospital, the subjects were entered into categories of positive result of *rapid test Amnioquick Plus 2* examination.

The collected data were coded, tabulated, and entered into the computer. A categorical-scale variable such as age, gestational age, diagnosis and other variables were then presented as frequency and percentage distribution. Diagnostic values (sensitivity, specificity, positive predictive value, negative predictive value, diagnostic efficiency, positive likelihood ratio and negative likelihood ratio) were calculated using a 2 x 2 table.

The standard examination conducted for determining PROM diagnosis was based on at least 2 positive examination results of either the existence of vaginal pooling in vaginal speculum examination, positive litmus paper test, the existence of ferning body in the vaginal secretion microscopic examination and the existence of certain substance in the amniotic fluid which may be detected by *rapid test*.[5,6] The confidentiality of the patients was protected by changing subjects' name with a code/initial or number; and all patients' data and anything related to this research would be treated as confidential. This research has obtained ethical approval from the Ethical Team of Dr. Soetomo Hospital, Surabaya.

RESULTS

The total number of pregnant women receiving standard examination was 52 subjects, consisting of 33 PROM pregnant women, and 19 non-PROM pregnant women. Data concerning the characteristics of our subjects can be seen in Table 1.

The average age of the PROM group was 28.70 years old, with a range from 20 to 40 years old. Meanwhile, the average age of the non-PROM group was 28.68 years old with a range from 19 to 41 years. The average gestational age of the PROM pregnant women was 35.64 weeks, with a range of 27 to 40 weeks; while for the non-PROM pregnant women was 32.89 weeks, with a range of 20 to 40 weeks. The average parity was 2 in the PROM group and 1.84 in the non-PROM group. The average estimated fetal weight for the PROM group was 2,530.30 gram with a range of 1,000 to 3,500 gram. The average estimated fetal weight of the non-PROM group was 1,873.68 gram with a range of 900 to 3,600 gram. The fundal height for the PROM group was 29.33 cm in average, while it was averaged to be 26 cm for the non-PROM group. There was no significant difference in the maternal age, gestational age, parity, estimated fetal weight and fundal height between the PROM and non-PROM group (p > 0.05). This indicated that both groups were homogeneous based on those aspects.

Table 1. Characteristics of Research Samples

Characteristics	PROM (n=33)		Non-PROM (n=19)		*p*-value
	Range	Average ± SD	Range	Average ± SD	
Age (years)	20-44	28.70 ± 5.14	19-41	28.68 ± 6.74	0.99
Gestational age (weeks)	27-40	35.64 ± 3.83	20-40	32.89 ± 4.99	0.61
Parity	1-5	2.03 ± 1.35	1-4	1.84 ± 0.89	0.59
Estimated fetal weight (gram)	1000-3500	2530.30 ± 810.66	900-3600	1873.68 ± 879.92	0.09
Fundal height (cm)	21-36	29.33 ± 4.56	18-35	26 ± 4.77	0.16

Table 2. The Results of *Amnioquick rapid test* and *Amnioquick Plus 2* Examination in the PROM and Non-PROM Groups

Examination	PROM (n=33)		Non-PROM (n=19)	
	True Positive (%)	False Negative (%)	False Positive (%)	Negative (%)
Amnioquick	28 (84.8)	5 (15.2)	1 (5.3)	18 (94.7)
Amnioquick Plus 2	30 (90.9)	3 (14.3)	1 (5.3)	18 (94.7)

The examination by *Amnioquick rapid test* showed no invalid result. The results of *Amnioquick rapid test* examination in PROM pregnant women showed a true positive for 28 women (84.8%) and false negative for 5 women (15.2%). The *Amnioquick rapid test* examination in non-PROM pregnant women showed negative for 18 women (94.7%) and false positive for 1 woman (5.3%).

The result of *Amnioquick Plus 2 rapid test* examination in PROM showed a true positive for 30 cases (90.9%) and false negative for 3 cases (14.3%). The *Amnioquick Plus 2 rapid test* examination in non-PROM pregnant women showed negative for 18 cases (94.7%) and false positive for 1 case (5.3%).

The diagnostic value of *Amnioquick rapid test* to detect PROM diagnosis showed an 85% sensitivity, 95% specificity, 97% positive predictive value, 78% negative predictive value, 86.8% diagnostic efficiency, 16.12 positive likelihood ratio and 0.16 negative likelihood ratio.

The diagnostic value of *Amnioquick Plus 2 rapid test* to detect PROM showed a 91% sensitivty, 95% specificity, 97% positive predictive value, 86% negative predictive value, 92.3% diagnostic efficiency, 17.27 positive likelihood ratio and 0.10 negative likelihood ratio.

Amnioquick Plus 2 was found to have a higher sensitivity, negative predictive value, diagnostic efficiency and positive likelihood ratio than the *Amnioquick rapid test*. The specificity and negative predictive value of *Amnioquick* and *Amnioquick Plus 2* was similar (95% and 97%), while the negative likelihood ratio of *Amnioquick Plus 2* was lower than *Amnioquick*.

The examination using *Amnioquick rapid test* showed a significant correlation at r=0.772 (p=0.000) when related to standard PROM examination. Likewise, the examination using *Amnioquick Plus 2 rapid test* showed a significant correlation at r=0.841 (p=0.000) when related to standard PROM examination. However, the correlation co-efficient value of *Amnioquick Plus 2* was higher than the *Amnioquick*.

DISCUSSION

PROM is often related to the morbidity of maternal and perinatal infection. Clinicians need to consider whether pregnancy will be maintained or not based on the possible risks for the mother and fetus in the management of PROM. The failure to establish PROM diagnosis may lead to the misapplication of standard PROM managements. On the contrary, an inappropriate PROM diagnosis establishment may cause mismanagement such as unnecessary hospitalization and labor induction. The establishment of PROM diagnosis is very important to avoid serious complications to the mother and fetus.[7-9]

Clinical diagnosis of PROM can simply be established if the pregnant woman complained of significant discharge of vaginal fluid or fluid leaking from the vaginal cervix. Clinicians are still doubting the establishment of PROM diagnosis based on anamnesis and speculum examination in 47% of cases. The PROM diagnosis is hard to establish if the vaginal discharge is little or only leaking. Another non-invasive examination may be needed to establish PROM diagnosis.[4,10] In our study, the subjects were divided into 2 groups, namely the PROM and the non-PROM group. There was no significant differ-

Table 3. The Diagnostic Value of *Amnioquick* and *Amnioquick Plus 2* with Standard PROM Examination in PROM

Diagnostic Test	Amnioquick	95% Confidence Interval	Amnioquick Plus 2	95% Confidence Interval
Sensitivity	85 %	73 - 97 %	91 %	81 - 100 %
Specificity	95 %	85 - 100 %	95 %	85 - 100 %
Positive predictive value	97 %	90 - 100 %	97 %	91 - 100 %
Negative predictive value	78 %	61 - 95 %	86 %	71 - 100 %
Diagnostic efficiency	86.8 %	-	92.3 %	-
Positive likelihood ratio	16.12	2.38 - 109.21	17.27	2.56 - 116.73
Negative likelihood ratio	0.16	0.07 - 0.36	0.10	0.03 - 0.28

ence between both groups in terms of the maternal age, gestational age, parity, estimated fetal weight, and the fundal height, so that the both groups could be considered as homogeneous.

The IGFBP-1 detection in the vaginal fluid using *Amnioquick rapid test*, which is considered a one-step bedside test, was deemed to produce a better sensitivity and specificity. Vaginal infections, medications, urine or seminal fluid show no effect on *Amnioquick rapid test*, unlike in litmus paper test. In this study, the false positive value of *Amnioquick rapid test* was 5.3%, compared to the previous research of 17.3%. Excessive vaginal bleeding may contribute to more positive result due to the IGFBP-1 which can also be found in blood.[11,12]

The IGFBP-1 level is generally equal in the cervical and vaginal fluid in the first trimester of pregnancy, but the IGFBP-1 level in the cervical fluid is two-times higher than the vaginal fluid in the second trimester. This implicates that the sampling site has an effect on the IGFBP-1 level in the genital tract if a swab is used in the sampling process. The *Amnioquick rapid test* showed a false negative of 15.2%, compared to the false negative number of 10.7% of IGFBP-1 in the previous research. This may be attributable to the inaccurate sampling site of vaginal swab, which should ideally be in the posterior vaginal fornix.[13,14]

The use of IGFBP-1 and AFP combination in a kit (*Amnioquick Plus 2*) is intended to increase the sensitivity and specificity. The IGFBP-1 line is set on a lower sensitivity to detect IGFBP-1 at a level of 10 ng/ml in order to produce a higher specificity. The AFP line is set on a higher sensitivity to detect AFP level of 5 ng/ml, allowing for a more sensitive and specific result at a gestational age of more than 38 weeks. The IGFBP-1 becomes less specific and the AFP becomes more specific when the pregnancy is after 38 weeks due to increasing IGFBP-1 level along with cervical maturation, resulting in a false positive result. This was concordant with the result of this research, where false positive value of *Amnioquick Plus 2 rapid test* was found to be low (5.3%). As noted previously, the false positive result can also be caused by blood. In this study, the false negative result of *Amnioquick Plus 2 rapid test* was 14.8% which may be caused by the less-appropriate sampling site of vaginal swab, the long time lapse between sampling and the time amniotic membrane was ruptured (more than 12 hours) so that the flow of amniotic fluid have stopped, and the declining

AFP level in the amniotic fluid during pregnancy at an age of more than 39 weeks.[15,16]

In this study, *Amnioquick rapid test* was more sensitive and specific in diagnosing PROM compared to the litmus paper test and ferning test. The sensitvity and specificity of *Amnioquick rapid test* was 85% and 95%, respectively. The sensitivity and specificity of *Amnioquick rapid test* was better than that of the litmus paper test (88% dan 74%, respectively) and ferning test (82% and 95%, respectively). The positive predictive value and negative predictive value of *Amnioquick rapid test* was 97% and 78%, better than the positive predictive value and negative predictive value of the litmus paper test (85% and 78%, respectively) and ferning test (96% and 75%, respectively). The positive likelihood ratio of the *Amnioquick rapid test* was 16.12, while the litmus paper test was 3.34, and ferning test was 15.55, which means that the examination showed a possible PROM diagnosis result respectively at 16.12 times, 3.34 times and 15.55 times compared to non-PROM. The negative likelihood ratio of the *Amnioquick rapid test* was 0.16, the litmus paper test 0.16 and the ferning test 0.19.

Dilbaz et al found that the sensitivity of IGFBP-1 in detecting PROM was 88%, with 81% specificity, 79% positive predictive value and 90% negative predictive value. They concluded that the IGFBP-1 strip test is a reliable test in diagnosing PROM, even for preterm PROM cases, as well as for confirming clinical diagnosis.[12]

Erdemoglu et al stated that the IGFBP-1 detection test has a sensitivity equal to the litmus paper test (97%) but was more specific (97% vs 16%) and accurate (97% vs 56%) in diagnosing PROM. Another research showed that in several cases, the diagnosis of PROM is hard to establish in a clinical way and the IGFBP-1 examination in the cervical and vaginal secretion using a dipstick quick test showed a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 92%, 84%, and 100%, respectively.[11,17]

The IGFBP-1 concentration in amniotic fluid is 100 to 1000 times higher than in serum. The *Amnioquick rapid test* relies on immunochromatography (ICT) with the principle of using monoclonal antibody against the human IGFBP-1. The *Amnioquick rapid test* shows a positive result for PROM if the sample contains at least 10 ng/ml IGFBP-1, so that it will give a more specific result. This is in accordance with our result, which shows a high specificity value of *Amnioquick rapid test* (97%).

In this study, the *Amnioquick Plus 2 rapid test* is more sensitive and specific in diagnosing PROM compared to the litmus paper test and ferning test. The sensitivity and specificity of *Amnioquick Plus 2 rapid test* was 91% and 95%, respectively, higher than the sensitivity and specificity of the litmus paper test and ferning test. The positive predictive value and negative predictive value of *Amnioquick Plus 2 rapid test* was 97% and 86% respectively, also higher than the positive predictive value and negative predictive value of litmus paper test and ferning test. The positive predictive value of *Amnioquick Plus 2 rapid test* was 97%, meaning that if the test shows a positive result, it will predict 97% of PROM. The negative predictive value of *Amnioquick Plus 2 rapid test* is also very useful for screening, which means that if the result using *Amnioquick Plus 2 rapid test* was negative, it will predict 86% of non-PROM.

The PROM diagnosis by ICT method to detect AFP has an accuracy of 97.8%, sensitivity of 97.9% and specificity of 97.8%. Another research showed that using a dipstick test to detect IGFBP-1 and AFP combination in the vaginal fluid had a sensitivity and specificity of 90.91%, and 97.10%, respectively. This was almost the same with the result using *Amnioquick Plus 2 rapid test* in our study.[18,19]

The sensitivity and specificity of *Amnioquick Plus 2 rapid test* is higher than that of the *Amnioquick rapid test* because the *Amnioquick Plus 2* uses two indicators namely IGFBP-1 and AFP. The IGFBP-1 is more specific in detecting PROM in gestational age of less than 38 weeks, meanwhile the AFP is more specific in detecting PROM in gestational age of more than 38 weeks making up for the increasing level of IGFBP-1 in the vaginal fluid as the cervix matures, which may give a false positive result.

The higher sensitivity and specificity of *Amnioquick* and *Amnioquick Plus 2 rapid tests* may assist in establishing the PROM diagnosis, especially in cases where the diagnosis is doubtful. The examination using *Amnioquick* and *Amnioquick Plus 2 rapid tests* should follow the procedure in the kit guidelines in order to minimize the possibility of false positive and false negative results.

The *Amnioquick* and *Amnioquick Plus 2 rapid tests* both have a strong and significant correlation with standard PROM examination. In our study, the *Amnioquick*, *Amnioquick Plus 2 rapid test*, and standard PROM examination are conducted on the same subjects so that the correlation coefficient can be comparable. The correlation coefficient of *Amnioquick Plus 2* is higher than the *Amnioquick rapid test*. Thus, it can be stated that the *Amnioquick Plus 2 rapid test* is better than the *Amnioquick rapid test*, such being our hypothesis in this study.

CONCLUSION

The *Amnioquick rapid test* compared to the standard PROM examination has an 85% sensitivity, 95% specificity, 97% positive predictive value, 78% negative predictive value, 86.8% diagnostic efficiency, 16.12 positive likelihood ratio, and 0.16 negative likelihood ratio. The *Amnioquick Plus 2 rapid test*, compared to the standard PROM examination, has a 91% sensitivity, 95% specificity, 97% positive predictive value, 86% negative predictive value, 92.3% diagnostic efficiency, 17.27 positive likelihood ratio, and 0.10 negative likelihood ratio. The correlation of *Amnioquick Plus 2* to the standard PROM examination is stronger compared to that of *Amnioquick rapid test*.

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