Research Article

Fetal Fibronectin (fFN) on the Imminent Premature Parturition in Correlation with Incidence of Preterm Labor

Fibronektin Fetus (fFN) pada Partus Prematurus Imminen dengan Kejadian Persalinan Prematur

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Abstract

Objective: To determine the relationship of fFn levels in cervicovaginal discharge of pregnant women who experience imminent premature parturition with the incidence of preterm labor.

Method: The study was carried out with Analytic Observational Prospective Cohort using cervicovaginal discharge of pregnant women that experienced imminent premature parturition taken from the delivery room of Obstetrics and Gynecology department dr. Saiful Anwar Hospital, Malang as well as Bangil Hospital and Ngudi Waluyo Wlingi Hospital. Statistical analysis was performed using the Shapiro-Wilk test and comparison test used independent samples t test for normal data, Mann-Whitney test if not. All analysis used SPSS for Windows 19.0 software.

Result: Thirty two patient samples was examined, 14 patients (43.75%) were primigravida and 18 patients (52.56%) is multigravida. 17 of these patients (53.13%) experienced aterm labor and 15 patients (46.87%) experienced preterm labor. Mann-Whitney test of the mean fFN levels between the aterm group (13.01 ± 7.57 ng/ml) and the preterm group (56.29 ± 27.77 ng/ml) showed a significant difference (p-value = 0.000 > 0.05). Moreover, Spearman's Rho correlation test also showed a strong correlation between fFN level and incidence of preterm labor (R = 0.797, p < 0.05).

Conclusion: fFN levels is significantly increase in cervicovaginal discharge from pregnant women with imminent premature parturition who experience preterm labor than pregnant women who experience aterm labor. Therefore, this result suggests that fFN has potential ability to become useful modality in preterm labor diagnosis.

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Keywords: cervicovaginal discharge, fFN, imminent premature parturition, preterm labor

Abstrak

Tujuan: *Mengetahui hubungan kadar fFN dalam sekret serviks dan vagina ibu hamil yang mengalami partus prematurus imminen dengan kejadian persalinan prematur.*

Metode: *Penelitian ini dilaksanakan secara Observasional Analitik dalam bentuk Kohort Prospektif menggunakan secret cervicovaginal wanita hamil yang mengalami partus prematurus imminen yang diambil dari kamar bersalin SMF Obstetri dan Ginekologi RSUD dr. Saiful Anwar Malang, RSUD Bangil serta RSUD Ngudi Waluyo Wlingi. Analisis statistik dilakukan dengan uji normalitas data sampel dengan uji Shapiro-Wilk, uji komparasi menggunakan uji t sampel bebas (independent sample t test) jika data terdistribusi normal, tetapi jika tidak maka digunakan uji Mann-Whitney. Semua penghitungan dilakukan dengan bantuan piranti lunak (software) SPSS for Windows 19.0.*

Hasil: *Dari jumlah total 32 sampel pasien yang diperiksa, 14 pasien (43,75%) merupakan primigravida dan 18 pasien (56,25%) merupakan multigravida. Dari pasien tersebut 17 diantaranya (53,13%) mengalami persalinan aterm dan 15 pasien (46,87%) mengalami persalinan prematur. Uji Mann-Whitney dari rerata kadar fFN antara kelompok aterm (13,01 ± 7,57 ng/ml) dan kelompok prematur (56,29 ± 27,77 ng/ml) menunjukkan perbedaan yang signifikan (p-value = 0,000<0,05). Hasil uji korelasi Spearman's Rho juga menunjukkan adanya hubungan yang kuat antara kadar fFN dengan kejadian persalinan prematur (R = 0,797, p < 0,05).*

Kesimpulan: *Kadar fFN mengalami peningkatan secara signifikan pada sekret serviks dan vaginal dari pasien dengan partus prematurus imminen yang mengalami persalinan prematur dibandingkan dengan yang mengalami persalinan aterm. Oleh karena itu, hasil ini menunjukkan fFN memiliki potensi untuk menjadi modalitas yang berguna dalam diagnosis persalinan prematur.*

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Kata kunci: *fFN, partus prematur imminen, persalinan prematur, sekret serviks dan vagina*

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INTRODUCTION

Preterm labor was defined as a delivery before 37 weeks' gestation. Preterm labor is still a major problem in obstetrics and 30% of cases occur with preterm premature rupture of membranes (PPROM).[1] Based on the health surveys of households conducted by the Ministry of Health said that the infant mortality rate as a result of premature birth in the Southeast Asia countries reached approximately 3 million cases annually, while in Indonesia the case of infant mortality is about 46 cases of 1000 live births in which preterm labor is

one of the main causes of the higher rate in prenatal mortality.[2] Although there is some intervention to prevent this, the incidence of preterm birth continues to rise. Premature parturition occurs in 7-12% of all pregnancies, in which three quarter of them associated with spontaneous labor.[3]

The incidence of preterm labor with or without rupture of membranes can be predicted through several ways including: measurement of IL-6 in the amniotic fluid which is increase in the incidence of preterm labor and collagen mRNA expression in amnion and chorion tissue which affects the threshold of ruptured membranes. Calculate the levels of MMP-8 in amniotic fluid, which is associated with increased amniochorionic infection that correlated with the occurrence of preterm labor. The predictors of preterm delivery above have good predictive value but very invasive, therefore it is necessary to find an alternative method in predict the incidence of preterm labor that are not invasive and has good predictive value as well. Fetal fibronectin (fFN) test and cervical scan has been investigated as a predictor for premature parturition.[4]

fFN is one of the most frequent biochemical parameters used to predict the risk of premature parturition and the success rate has been proven in a randomized controlled study in symptomatic and asymptomatic women. fFN test value lies in its high negative predictive value.[4]

Fibronectin is a glycoprotein with high molecular weight which can be found in body fluids such as plasma and extracellular matrix. This substance is derived from amniotic fluid, placental tissue and malignant cells which is responsible for managing a variety of biological functions, including coagulation and bacterial opsonization. fFN express an oncofetal domain.[3] fFN serve as "biological adhesive" that helps to attach the fetal chorionic membrane with maternal decidua.[5] In early pregnancy, when gestational saccus attached to the uterine wall, presence of fFN in cervicovaginal secretions are a normal condition. When choriodecidual surface has joined around 20-22 weeks, presence of fFN in this cervicovaginal discharge is not physiological. This may be caused by inflammation or disruption mechanism in the placenta or fetal membranes.[3] Measurement levels of fFN in cervicovaginal secretions of pregnant women who experience imminent premature parturition (IPP) is a non-invasive method to predict the incidence of preterm labor and the prediction of other pathological conditions.[6]

This research aim to investigate the relationship between fFN levels in cervicovaginal secretions of pregnant women who have IPP with the incidence of preterm birth in the delivery room and obstetric ward at Dr. Saiful Anwar Malang hospital, Bangil hospital as well as Ngudi Waluyo Wlingi hospital.

METHODS

Subjects Selection

The inclusion criteria for this study were: pregnant women with gestational age of 30 weeks to 34 weeks experienced an imminent premature parturition, not accompanied by intrauterine infection according to Gibbs criteria which require termination of pregnancy, fetal congenital abnormalities, deformities of the uterus, antepartum hemorrhage, preeclampsia, eclampsia, gemeli and polyhydramnios, willing to follow the study. Exclusion criteria for this study were: pregnant women with imminent premature parturition but rejected to receive standard therapies, with cervical manipulation or have sexual intercourse within 24 hours before admission, have ruptured membranes, accompanied by non-obstetric medical complications.

Measurement of Fibronectin Fetus

Terms of specimen retrieval

Intact amniotic membrane, minimum cervical dilatation (<3 cm) and sampling was not performed at the gestational age < 30 weeks and > 34 weeks.

Taking specimen

Specimens taken from the posterior vaginal fornix while performed sterile speculum examination (before performed another procedure such as digital cervical examination, vaginal ultrasound, etc.) Specimens taken by Adeza Biomedical Specimen Collection Kit in the form of polyester tipped swab (Dacron swab). Swab is inserted into the vagina and turn lightly along the posterior fornix for about 10 seconds to absorb the cervicovaginal secretions. After that, remove the swab from the vagina carefully and place it in a tube that has been filled with fluid buffer (packet Specimen Collection Kit) until the tip of Dacron submerged. Break the swab on the sign holder stems available. Make sure the rest of the rod just about the tube and close the tube

tightly. Give label Specimen Transport Tube. If the sample is not immediately checked, immediately put in the refrigerator.

Measurement Levels of fFN (Fetal Fibronectin Enzyme Immunoassay)

The principle is to use the ELISA examination. Prepare all reagents and samples. Put 100 µl sample and 100 µl standard liquid into a micro titer well. Cover with the adhesive strip provided. Samples were incubated in a micro titer well were plated FDC-6 (monoclonal antibody) for 2 h in the temperature of 37°C. Dispose of water from each well. Add 100 µL Biotin antibody (1x) in each well. Cover with a new adhesive strip. Incubate for 1 hour in a 37°C temperature. Warm to room temperature and mix gently until solution appears homogeneous. Aspirate from each well and then wash, reprocess a sample of 2x and 3x leached standards. Washing is by filling each well with Wash Buffer (200 µL) using a squirt bottle, multi-channel pipette, manifold dispenser, or auto washer and let stand for 2 minutes. After the waste until completely clean. After the last wash, wash all of the wash buffer by aspirating ordecanting. Turn well and stick to clean blotting paper. Add 100 µL avid in HRP (1x) in each well. Close microtiter new adhesive strip. Then Incubate for 1 hour at a temperature of 37°C. Repeat the process of washing and aspiration as much as 5 times. Add 90 µL of TMB substrate to each well. Incubasition for 15-30 minutes at a temperature of 37°C. Keep it away from light. Add 50 µL Stop Solution to each well, and tap-tap the plate gently to mix the solution. After that the samples were examined with a spectrophotometer at a 550 nm wavelength to determine the concentration of fetal fibronectin.

Data Analysis

In this study, the data analysis techniques used namely normality test sample data with the Shapiro-Wilk test, comparison test used independent samples t test (independent sample t test) if the data were normally distributed, but if not then used Mann-Whitney test. All calculations performed in software SPSS for Windows 19.0.

RESULTS

Characteristics of study subjects based on parity/ pregnancy status can be seen in Table 1.

Table 1. Pregnancy Status Frequency Distribution

Pregnancy status	Frequency	Percentage
Primigravida	14	43.75 (%)
Multigravida	18	56.25 (%)
Total	32	100 (%)

From the table above, it appears that the subjects are scattered by parity/pregnancy status among primigravida group consisted of 14 people (43.75%) and multigravida group consisted of 18 (56.25%).

Characteristics of study subjects based on age can be seen in Table 2 below.

Table 2. Age Frequency Distribution of Subjects

Age (yo)	Frequency	Percentage
< 20	10	31.25 (%)
20-35	17	53.12 (%)
> 35	5	15.63 (%)
Total	32	100 (%)

From the table above it is known that the study subjects scattered in the age group < 20 years old were 10 people (31.25%), age group 20-35 years were 17 (53.12%) and the age group > 35 years were 5 people (15.63%). Characteristics of study subjects based on the incidence of preterm and aterm delivery presented in Table 3 below.

Table 3. Occurrence of Labor Frequency Distribution

Occurrence of labor	Frequency	Percentage
Aterm	17	53.13 (%)
Preterm	15	46.87 (%)
Total	32	100 (%)

From the table above it appears that the study subjects are scattered among the groups based on the occurrence of aterm labor consisted of 17 people (53.13%) and preterm group consisted of 15 people (46.87%).

Parametric Test

In this study, the results of data analysis on the normality test performed using the Shapiro-Wilk test. The decision criteria, i.e when the Sig or p-value is greater than $\alpha = 0.05$ thus the data is nor-

mally distributed, while the Sig or the p-value is smaller than $\alpha = 0.05$, the data were not normally distributed. If the data were normally distributed, the comparison test used independent samples t test. Meanwhile, when the data were not normally distributed, the comparison test used Mann-Whitney test. Shapiro-Wilk test analysis showed that subjects age data (years old) in the aterm group (p-value = 0.114>0.05), and the preterm group (p-value = 0.783>0.05), p-value indicates the value greater than the significance level $\alpha = 0.05$. So the subject age data has proved to be normally distributed, therefore it were analyzed using independent samples t test. While fFN levels (ng/ml) in aterm group (p-value = 0.005<0.05) and preterm group (p-value = 0.031<0.05), p-value indicates the value is smaller than the significance level $\alpha = 0.05$. So fFN levels data were not normally distributed and therefore it were analyzed using the Mann-Whitney test to prove the research hypothesis.

Comparison Test Results of Subjects Age

In the comparison test results for age (years) based on the occurrence of labor between aterm group (n = 17) and preterm group (n = 15) using independent samples t test briefly described and shown in the table below. Based on the results of independent samples t-test showed that there was no significant difference (p-value = 0.445>0.05), the mean age of the study subjects, between aterm group (25.24 ± 7.97 years) and the preterm group (7.27 ± 27.33 years). It is explain that age of subjects spread evenly based on the incidence of labor between aterm group and preterm group.

Comparison Test Results of fFN Levels

In the comparison test results of fFN levels (ng/ml) based on the occurrence of labor between aterm group (n = 17) and preterm group (n = 15) using the Mann-Whitney test briefly described and shown in the table above. Based on the results of the Mann-Whitney test showed that there was a highly significant difference (p-value = 0.000<0.05) between the mean levels of fFN (ng/ml) in aterm group (13.01 ± 7.57 ng/ml) and preterm group (56.29 ± 27.77 ng/ml). It is showed that subjects with incidence of preterm birth showed higher levels of fFN compared to subjects with aterm labor.

Comparison test results of fFN levels (ng/ml) based on pregnancy parity/status between primigravida group (n = 14) and multigravida group (n = 18) using the Mann-Whitney test briefly described and shown in the table below. Based on the results of the Mann-Whitney test, it is showed that there was no significant difference of subjects fFN levels (ng/ml) (p-value = 0.000 <0.05) among primigravida group (28.46 ± 25.45 ng/ml) and multigravida group (37.06 ± 32.21 ng/ml). However, based on the average value of the fFN levels, subjects with multigravida tend to be higher compared with subjects in the primigravida, although this difference was not statistically significant.

Correlation Test Results of fFN Levels with Incidence of Preterm labor

Based on the data analysis from Spearman's rho correlation test, occurance of labor with fFN levels in the study sample (n = 32) briefly described and shown in the table below. There was a highly significant relationship between the occurrence of labor with fFN level (p-value = < 0.000) on research subjects (n = 32) with strong relationship (correlation coefficient = 0.797). Positive value (0.797) indicates there is a very strong relationship between the two variables, i.e increase in the fFN levels was related to increase of preterm labor, and so did the other hand, when there is a reduction in the incidence of preterm labor, fFN would also decreased.

DISCUSSION

Fibronectin (FN) is a glycoprotein dimer with a molecular weight of 440 k Da. There are two types of FN, i.e soluble FN (soluble plasma fibronectin) which is the main protein in plasma (300 pg/ml) produced by hepatocytes in the liver cells and insoluble FN (insoluble cellular fibronectin), which is the main component of the extracellular matrix produced by various cells, especially fibroblasts and other cells such as chorion, membrane basalis and some cancer cells.[7] Fetal fibronectin (fFN) included in the large glycoprotein with a molecular weight produced by chorionic membranes during pregnancy and at desidua basalis near intervilli space. fFN is a major component of the extracellular matrix amniotic membrane.[3,8] fFN is important in embryogenesis, especially in the process of cell adhesion and migration during embryo development.[9] fFN can be detected in the connective tissue of the fetus, placental tissue and amniotic tissue. fFN generally can also be found in cervicovaginal

discharge until 20 weeks gestational age but are no longer found in gestational age from 24 to 34 weeks because of a consolidation uteroplacental junction and the formation of amniotic membrane is already perfect. Occurrences of fFN in 24-34 weeks showed the presence of leakage or disintegration fFN from uteroplacental junction that indicating a pathologic separation condition between the fetal's membrane with maternal decidua or fetal membrane rupture that exposed fFN from amniotic fluid to cervicovaginal discharge. Besides, the fFN in cervicovaginal discharge in symptomatic women with gestational age of 24-34 weeks, indicating high risk of imminent premature parturition.[10,11]

In this study, the fFN level of mother with aterm labor was 13.01 ± 7.57 ng/ml and in preterm labor was 56.29 ± 27.77 ng/ml. Measurement using the Mann - Whitney test showed that there were significant differences between the 2 groups (p = 0.000 p < 0.05). These findings correspond with the results of previous studies by Peaceman (2007), which showed that the detectable fFN in a significant level (> 50 ng/ml) showed an increased risk of preterm labor. The results also showed that the increase in the fFN level in cervicovaginal discharge caused by the fibronectin secretion during acute perturbation phase of the intrauterine area.[3] Another study by Schmitz (2006) showed that in pregnant women with fFN level > 50 ng/ml, there was a risk of getting labor before 35 weeks gestational age or in 7-14 days after fFN rate was detected.[11] This is also supported by research from Bolt (2011), which indicated that the mother with a short cervix size (<15 mm) and high fibronectin level (> 50 ng/ml) has a high risk factor for experiencing delivery before age 35 week.[12]

From the findings above, it was known that most (53%) of pregnant women with IPP have preterm labor and almost half (47%) of pregnant women with IPP were not have preterm labor (aterm). Theoretically, it can be mentioned that there were many cause of imminent premature parturition including infection, inflammation, hemorrhage, preeclampsia, eclampsia, trauma and other causes. Previous study showed that fFN not act directly as the cause of preterm labor in mothers with IPP. However, in several studies have shown that some mechanism that caused preterm labor like bleeding, eclampsia, preeclampsia, infection can trigger the occurrence of inflammation, which can cause increased expression of fFN in cervicovaginal discharge after a gestational age > 24 weeks. Research showed that pro-inflammatory cytokines such as TNF-α, IL-6, PAF (platelet activating factor), CRP (C-reactive protein) and nitric oxide can trigger softening and dilatation of the cervix, uterine contractions and begins the process of breaking the locker liquor, through activation of cyclooxygenase band in amniotic, chorionic, desidual and myometrium, increased infiltration of leukocytes, and stimulating the production of matrix metalloproteinase. Such a condition would induce the release of fetal tissue from decidua maternal and cervical thinning that caused leakage of fFN from uteroplacental junction and amniotic fluid into the cervicovaginal discharge. This reflects the separation of the chorionic layer of the uterus and detachment of decidual chorionic components in cervicovaginal discharge. This leakage will be followed by preterm delivery a few weeks afterwards.[2,6,13-15]

The results of this study indicated that the mother who experienced preterm labor had fFN level (56.29 ± 27.77) that significantly higher compared to mothers who had aterm labor (13.01 ± 7.57). This study was similar to several studies that showed whether mothers who experienced preterm labor had a high fFN level in fFN examination at 24-34 weeks gestational age.[11] This indicated that the fFN can play a role in predicting the occurrence of preterm labor in pregnant women who have an IPP.

In this study the findings indicated that there was a strong relationship between the fFN level in cervicovaginal discharge with occurrence of preterm labor. This was proved by an increase in the fFN level significantly (p = 0.000 p <0.05) in mothers with preterm labor compared to mothers with aterm labor. The Spearmen's rho correlation test also showed that the value of R = 0.797 (p = 0.000, p <0.05), which indicated a very strong relationship between the two variables. These results are in accordance with several previous studies that showed there was a strong relationship between the two variables. Research by Chandiramani (2011) showed that the fFN level and the length of the cervix could be used as a predictor of spontaneous preterm birth. This is also supported by Skoll study (2006) which indicated that the increase of fFN level in symptomatic women can be used to predict the likelihood of preterm labor.[16,17]

Various studies have been conducted to determine the role of fFN in the pathophysiology of pre-

term labor. Based on the majority of the research results, it is showed that the fFN had no direct role in causing the occurrence of preterm labor. Research by Yamani and Soliman in 2002 showed that an increase in Interleukin-1B and Interleukin-8 was believed to play a role in increasing the fFN level in mother with preterm labor. Another study by Jacobsson (2003) showed that other pro inflammatory cytokines such as Interleukin-6 and Tumor Necrosis Factor-α (TNF-α) also play a role in increasing fFN level. This could happen because of an inflammatory process in mothers with preterm labor is caused by various mechanisms, particularly as a result of infection, allergic phenomena or excessive uterine distention.[18,19]

Important role of fFN as a good predictor for preterm labor has been shown in several previous study but its role as direct cause of preterm labor is remain controversial. Interestingly, recent study by Mogami (2012) showed that it has the potential to not only act as a predictor of the occurrence of preterm delivery, but could have a direct role in the process. Administration of fFN in vitro on amniotic cells can induce a rise in expression of MMP-1 and MMP-9 and increased synthesis of COX-2 and Prostraglandin-E2. It is believed to play an important role in inducing the occurrence of Preterm Premature Rupture of Membranes (PPROM) and excessive contractions of the uterus that can cause the occurrence of preterm labor. This study is strengthened by the occurrence of preterm labor in pregnant mice after being injected with fFN. These results provide a new picture of fFN role in the pathogenesis of preterm labor and the process is likely to happen given the significant increase of fFN level in the mother with imminent premature parturition that experienced preterm labor, as shown in the results of this study. However, further research was needed to prove the role of fFN in induced preterm labor in humans.[20,21]

CONCLUSION

fFN levels is significantly increase in cervicovaginal discharge from pregnant women with imminent premature parturition who experience preterm labor than pregnant women who experience aterm labor. Therefore, this result suggest that fFN has potential ability to become useful modality in preterm labor diagnosis.

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