Comparison Of *Progesterone-Induced Blocking Factor* Serum Levels In Preterm Labor And Preterm Pregnancy

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ABSTRAK

Persalinan kurang bulan merupakan fenomena multifaktor yang melibatkan proses inflamasi yang akan mempengaruhi keseimbangan imunologis rasio Th1 terhadap Th2 yaitu meningkatkan dominansi sitokin proinflamasi Th1 dan juga memicu terjadinya *functional progesterone withdrawal*.

Progesteron berguna dalam mempertahankan uterus selama kehamilan dalam keadaan relaksasi dan proses persalinan dipicu oleh *progesterone withdrawal*. Selain itu, progesteron mempunyai efek antiinflamasi dan imunomodulator. Meskipun telah diduga bahwa efek progesteron pada tatalaksana persalinan kurang bulan dihubungkan dengan efek antiinflamasinya, namun mekanisme kerja yang spesifik belum diketahui secara pasti.

Efek biologis progesteron diperantarai oleh protein berukuran 34 kDa yang dikenal sebagai *progesterone-induced blocking factor* (PIBF) yang disintesis oleh limfosit wanita hamil yang sehat di bawah pengaruh progesteron. PIBF akan menghambat produksi asam arakidonat, mengurangi aktivitas sel NK, dan memodulasi keseimbangan sitokin.

Penelitian ini merupakan penelitian analitik komparatif dengan desain potong silang yang membandingkan kadar PIBF serum antara persalinan kurang bulan dengan kehamilan kurang bulan. Setiap kelompok terdiri atas 16 orang yang memenuhi kriteria inklusi yang berobat ke RSUP Dr. Hasan Sadikin Bandung serta rumah sakit jejaring, berlangsung dari bulan Juli-November 2013. Kadar PIBF serum diukur dengan menggunakan teknik *enzyme-linked immunosorbent assay* (ELISA).

Terdapat perbedaan bermakna antara kadar PIBF serum persalinan kurang bulan (1021,162 ± 391,4051 ng/mL) dengan kehamilan kurang bulan (1297,675 ± 174,2165 ng/mL) dengan nilai p = 0,029. Disimpulkan bahwa kadar PIBF serum persalinan kurang bulan lebih rendah dibandingkan pada kehamilan kurang bulan.

Kata kunci : PIBF, persalinan kurang bulan, progesteron

ABSTRACT

Preterm labor is a multifactorial phenomenon involving inflammatory processes that will affect the balance of Th1 to Th2 by increasing dominance of pro-inflammatory Th1 cytokines and also lead to functional progesterone withdrawal.

Progesterone maintains pregnancy mainly by promoting myometrial quiescence and labor is initiated by progesterone withdrawal. Progesterone also has antiinflammatory properties and as an immunomodulator. While it has been postulated that the effect of progesterone on preterm birth is related to its anti-inflammatory properties, the spesific mechanism of action remains unclear.

The biological effects of progesterone are mediated by a 34-kDa protein named the progesterone-induced blocking factor (PIBF). PIBF is synthesized by lymphocytes of healthy pregnant women in the presence of progesterone. PIBF inhibits arachidonic acid production, reduced NK cell activity, and modifies the cytokine balance.

The objective of this study was to compare serum concentrations of PIBF of women with preterm labor with those women with normal pregnancy. A comparative analytical study with cross-sectional design was conducted. This study consisted of 16 women in each group. All the subjects met the inclusion criteria and were admitted to the Dr . Hasan Sadikin hospital and it's district hospital. This study conducted from July until November 2013. Serum PIBF concentrations were measured by enzyme-linked immunosorbent assay (ELISA) .

Mean PIBF concentrations in serum of patients with preterm labor were significantly lower (391.4051 ± 1021.162 ng/mL) than in those of normal pregnancy (174.2165 ± 1297.675 ng/mL) with p = 0.029 . It was concluded that the levels of serum PIBF preterm labor is lower than in normal pregnancy.

Keywords : PIBF, preterm labor, progesterone

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INTRODUCTION

Preterm delivery is multifactorial phenomenon. Lockwood suggests several factors contribute to preterm delivery, infection and inflammation, activation of the hypothalamic-pituitary-adrenal feto-maternal axis, decidual bleeding, and patological uterine distention.[1-4] These factors involve cytokines mediated inflammatory reactions.[5] Labor is an inflammation process. There is high levels of proinflammatory cytokines in preterm labor compared to term labor.[6] Infections, stress, and obesity can lead to inflammation.

Inflammation is one of the important mechanisms in the preterm and term labor. In term labor there is infiltration of inflammatory cells into the myometrium, cervix, membranes, and amniotic fluid as well as increased production of proinflammatory cytokines and chemokines.[7,8] Inflammation activates immunological mechanisms, such as Th1 and Th2 balance. Pregnancy will be maintained if Th2 dominates. Several studies of preterm labor found elevated levels of proinflammatory Th1 cytokines (IFN and IL-2), while healthy pregnant women have higher levels of anti-inflammatory Th2 cytokines (IL-4, IL-5, and IL-10).[9,10]

In preterm and term labor, there is evidence of increased inflammatory markers such as TNFα, IL-1, IL-6 and decreased of anti-inflammatory marker IL-10.[9,10] Inflammatory cytokines such as IL-1 and TNFα will increase the prostaglandins production, whereas IL-10 and progesterone will inhibit prostaglandin production.[11] Thus, progesterone may have an anti-inflammatory effect and therefore suspected a link between inflammatory processes, impaired progesterone receptor expression with the initiation of preterm labor. Progesterone role in threatened preterm labor appeared to be associated with antiinflammatory effects, but its mechanism of action is unclear.

Progesterone appears to be important in maintaining uterine quiescence and labor is triggered by functional progesterone withdrawal.[12] Many physiological and pathological state such as inflammation, infection, uterine distention, maternal or fetal stress, and fetal development can lead to functional progesterone withdrawal.[13]

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In the presence of progesterone, lymphocytes of pregnant women produce a protein, progesterone-induced blocking factor (PIBF).

This protein inhibits the natural killer cells (NK) activity directly or through inhibition of arachidonic acid metabolism, increasing the production of Th2 cytokines by shifting the balance toward Th2 dominance, and enhancing the formation of asymmetric antibodies.[10] In addition, progesterone suppresses IL-1β and IL-8 expression induced by NF-κB. Thus, progesterone is an immunosuppressant through suppression of NF-κB.[12,14]

PIBF concentration increased from 7th to 37th weeks' gestation in normal pregnancy. After 41 weeks gestation, PIBF concentration decreases dramatically. If PIBF concentration remains low, the risk of premature pregnancy termination will increase.[14] Women with threatened miscarriage or history of recurrent miscarriage have lower PIBF concentrations compared with normal pregnant women.[15,16] In addition, serum and urine levels of PIBF on threatened preterm labor also lower than in normal pregnant women.[15,18]

Raghupathy et al found that PIBF produced by lymphocytes of pregnant women increased the production of Th2 cytokines. PIBF has no effect of cytokine production by lymphocytes in non-pregnant women. It appears that PIBF is an important immunoregulator for the successful of pregnancy.[9]

METHODS

This was a cross-sectional study. Subjects were women experienced preterm labor at 20 to less than 37 weeks of gestational age hospitalized at Hasan Sadikin hospital and hospital network. The control group was obtained by matching the gestational age and parity with the subject.

Preterm labor is defined as regular uterine contractions (≥ 3x/10 minutes) with ≥ 4 cm cervical dilation and cervical effacement. Inclusion criteria were nulliparity, singleton, lived baby without abnormalities of fetal lie, intact membranes, no signs of infection (fever, leukocytes >25,000/mm^3, normal urinalysis result), no fluor albus, hypertension, heart disease, lung disease, diabetes mellitus, nor other chronic diseases, do not smoke, no obstetric complications, and there were no congenital abnormalities.

PIBF serum levels were measured using enzyme-linked immunosorbent assay (ELISA). Data analyzed using SPSS for Windows.

Student's T-test was used to compare mean value. If data were expressed as median, Mann-Whitney U-test was used.

RESULT

There were 32 subject included in this study. Sixteen subjects with preterm labor and 16 control group. Characteristics of subject with preterm labor and control group with preterm pregnancy can be found at table 1.

Table 1. Characteristic of study groups

		Preterm Labor n = 16	Control n = 16
Maternal age (years)			
	Mean ± SD	23,81 ± 5,480	27,88 ± 8,586
	Median	21,50	28,50
	Range	18 – 33	15 – 40
Parity			
	0	12 (75 %)	12 (75 %)
	1	4 (25 %)	4 (25 %)
Gestational age (weeks)			
	Mean ± SD	32,81 ± 2,373	32,81 ± 2,373
	Range	28 – 36	28 – 36

From table 2 found that median PIBF serum on preterm labor group were 1158,200 ng/mL significantly lower than control group 1285,450 ng/mL (p = 0,029).

PIBF serum levels (ng/mL)	Preterm Labor n = 16	Control n = 16	Statistical Result
Mean	1021,162	1297,675	Z = -2,186
SD	391,4051	174,2165	p = 0,029*
Median	1158,200	1285,450	

Table 2. Comparison of PIBF serum levels between preterm labor and preterm pregnancy
Note : z = *Mann-Whitney U* test
* = p < 0,05 (significant)

DISCUSSION

In this study, control group were matched to the subject group to reduce confounding factors. Matching the parity and gestational age were done between the two study groups. Polgar found PIBF concentration would increase up to 37 weeks of gestation and then decreases dramatically after 41 weeks gestation in normal pregnancy and was higher compared with patologic pregnancy.[14] Thus, matching method was expected to reduce bias due to differences in gestational age.

This study showed that mean PIBF serum levels in preterm labor were significantly lower than in preterm pregnancies (1021.163 ± 391.4051 vs. 1297.675 ± 174.2165, p = 0.029).

Hudic, et al showed that PIBF serum levels in threatened preterm labor were lower than in normal pregnancy (171.12 ± 162.06 ng/mL vs. 272.85 ± 114.87 ng/mL, p < 0.05).[17] Polgar, et al also found that PIBF levels in urine on threatened preterm labor group were lower than in normal pregnancy.[14]

PIBF is a 34 kD protein produced by lymphocytes of pregnant women under the influence of progesterone. In animal studies (guinea pig and armadillo), it was known that decreased systemic progesterone levels played an important role in the initiation of labor. While on human, progesterone concentration remains elevated until the placenta is delivered. In 1960, Csapo proposed an idea of functional progesterone withdrawal accompanied by increased ratio of 17β estradiol to progesterone in preterm labor.[18] Functional progesterone withdrawal will lead to changes in progesterone receptor expression in immune cells. Lymphocytes of pregnant women with threatened preterm labor had low expression of progesterone receptor therefore PIBF was lower than in healthy pregnant women.[19]

Research Raghupathy et al showed that PIBF worked on lymphocytes of pregnant women to increase the production of Th2 cytokines which are cytoprotective.[9] In addition, PIBF also induced asymmetric antibodies as well as inhibited NK cell degranulation.[20,21] PIBF appears to be an important immunoregulator for successful of pregnancy.

Low PIBF levels in preterm labor leads to increased production of pro-inflammatory cytokines therefore shifts the balance of Th1 to Th2 into Th1 dominance. Th1 proinflammatory cytokines would increase the expression of genes that regulate labor, oxytocin receptors, and prostaglandins production that cause uterine contractions and cervical effacement.[15,22]

PIBF modulates arachidonic acid metabolism by lowering prostaglandin and leukotriene synthesis. Low PIBF levels will increase prostaglandin production that plays role in the uterine contraction and cervical effacement and dilation. Low PIBF also increases leukotriene production that enhanced NK cell activity and inflammatory reaction.[15]

Various studies revealed significant benefits of progesterone administration for threatened preterm labor but its mechanism of action is unclear.[23-25] In this study, it was found that PIBF serum levels were lower in preterm labor. This suggested that if PIBF production can be increased, it was expected can prevent the occurrence of preterm labor.

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