The Correlation between Salivary Progesterone Level and the Incidence of Preterm Labor

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Abstract

Background: This study was conducted to determine whether salivary progesterone level correlated with the high risk incidence of preterm labor.

Method: This was an observational analytic study with a comparative cross-sectional design, comparing the level of progesterone in the preterm group to control group. The preterm group consists of 28-36 weeks pregnant women with the high risk of preterm labor and women with normal pregnancy as a control group. This study conducted from January to March 2019 at the Hasan Sadikin General Hospital Bandung. Saliva samples were taken and observations were made on the subject during conservative treatment at the hospital. Progesterone levels of both groups were examined by the Enzyme Linked Immunosorbent Assay (ELISA).

Results: The results showed that the average salivary progesterone level in the preterm group was 411.75 pg/ml while in the control group was 1082.54 pg/ml. There is a significant difference in the mean levels of progesterone between the two groups with a p value < 0.001.

Conclusion: There is a significant correlation between low salivary progesterone level and the incidence of preterm labor.

INTRODUCTION

Preterm labor is a labor occurs at 20 to 37 weeks pregnancy. It is a global problem and a second cause of neonatal mortality in the world with total 3.1 million neonatal death every year. The incidence of prematurity in developing countries still high, in India 30%, South Africa 15%, and Sudan 31%. The preterm birth in Asia is 6.907 every 1000 labor or approximately 6.2%, in South East Asia is 1.271 preterm birth every 1000 labor or approximately 11,1%. Based on data in 2010, Indonesia is in the fifth place in Asia with the preterm birth accounted 675.700 with the ratio 15.5% every 100 life birth and placed Indonesia in the ninth position from 184 countries in the world.[1-3]

Every year there were 4 million neonatal deaths. The cause of death includes prematurity (28%), neonatal sepsis (26%) and asphyxia (23%). Prematurity causes 12 times increase of anoxia risk and five times risk of intracranial bleeding than term labor. The basic research in 2007 described the etiology of neonatal death in 0-6 days group as respiration distress 36.9% followed by prematurity 32.4%. The causes of neonatal death in 7-28 days group are neonatal sepsis 20.5% and prematurity 12.8%.[4]

Progesterone responsible to maintains pregnancy and prevent prematurity through quiescence myometrium status maintenance. Onset of labor, term or preterm, is thought to be caused by the decrease of functional progesterone activity in uterine so the initiation of labor, myometrium contractility and excitability start to occur. Some studies found the increase of saliva estriol and progesterone level ratio before the onset of labor both of term and preterm accompanied by the decrease of progesterone level. Steroid concentration in saliva describes free unconjugated steroid and biologically active fraction of hormone in plasma so it can describe the progesterone level in the body. Salivary sample is easier to collect and more comfortable for patient so it is preferable than serum sample that consider as invasive procedure.[5-11]

Progesterone level in saliva could be considered as a predictor of a high risk preterm labor and identified the

sufficient patient in order to prevent the preterm labor and start the progesterone therapy earlier.[9,10]

METHODS

This is an observational cross-sectional study conducted from January to March 2019. Subjects were 28-36 weeks pregnant women with high risk preterm labor that came to delivery and emergency room of Obstetrics and Gynecology Department, Hasan Sadikin General Hospital (RSHS) Bandung, fulfilled the inclusion criteria, willing to participate in the study and signed the informed consent. Ethical approval number LB.02.01/X.6.5/10/2019 was given by Ethical Comitee of Hasan sadikin General Hospital on January 11, 2019.

Sample size was determined with the calculation to test the mean difference between two groups with confidence rate 95%, two tail hypothesis (Z_{α} = 1.96) and a power test 95% (Z_{β} = 1.65). By determining the prevalence of preterm birth by 20%, the study sample was determined as 100/20 x 13 = 68. Inclusion criteria were all parity and age, single life pregnancy, 28-36 weeks pregnancy, premature contraction and intact membrane. Women with obstetric difficulties like preeclampsia, antepartum hemorrhage, polyhidramnion, mental disorder, chronic disease like hypertension, heart disease, lung disease, diabetes mellitus and others, fetal congenital abnormality defined bu ultrasonography, urogenital tract infection, systemic infection and incompetent cervix were excluded from study sample.

Subjects who fulfilled the criteria were interviewed and filled questionaire consisting of sociodemography data documentation like age, the last day of period, work, parity and previous labor history. This was followed by external physical examination, cardiotocography and internal examination to determine cervical condition, transabdominal ultrasonography to detect fetal abnormality and to calculate cervix size as a diagnostic tool for preterm labor.

After all the examinations, 2-3 cc of saliva was taken from subject between 9 am to 8 pm, then the samples were refrigerated within 30 minutes after collection and freezed at -20oC for 4 hours. The progesterone level was calculated with ELISA method. Subjects were undergoing conservative treatment according to standard operational procedure of Hasan Sadikin Hospital and were given tocolytic nifedipine 20 mg three times a day and dexamethasone 6 mg intramuscular injection twice a day for two days and observed for pregnancy output. Subjects were discharged if the fetus was in good condition and uterine contractions dissapeared. Subjects who succeded in treatment were grouped as normal pregnancy and subjects who failed were included in the preterm group.

Data analysis consisted of descriptive and hypothesis analysis. Statistic analysis used SPSS with unpaired T test to compare the difference in mean of salivary progesterone level between preterm group and control group.

RESULTS

The participant of the study were divided into two groups, preterm group (P group) consisting of 17 women and control group (C group) consisting of 51 women. The characteristics included age, gravida, occupation, education and gestational age.

Table 1

Subject characteristics

Characteristic	Group		*p* value*
	P (n=17)	C (n=51)	
Age (in years)			**0.489**
< 20	4 (36.4 %)	7 (63.6%)	
20 – 35	12 (24.5%)	37 (75.5%)	
> 35	1 (12.5%)	7 (87.5%)	
Gravida Status			**0.387**
Gravida 1	10 (32.3%)	21 (67.7%)	
Gravida 2	4 (21.1%)	15 (78.9%)	
Gravida 3	3 (25%)	9 (75%)	
Gravida > 4	-	6 (100%)	
Occupation			**1.0**
Work	1 (25%)	3 (75 %)	
Not work	16 (25%)	48 (75%)	
Education			**0.736**
Elementary School	3 (17.6%)	14 (82.4%)	
High School	13 (27.7%)	34 (72.3%)	
University	1 (25%)	3 (75%)	
Gestational Age			**0.563**
Early preterm (28-33 weeks)	16(27.1%)	43(72.8%)	
Late preterm (>33 -36 weeks)	1(11.1%)	8(88.8%)	

P= preterm labor; C=control, * calculated with Chi-squared test, except for work with Fisher exact.

Based on table 1, there was no significant correlation between age, parity, occupation and education as confounding variables to preterm labor with p value > 0.05. Most of subjects have age range 20-35 years old, housewives, high school grade education and primipara.

Table 2

The comparation of salivary progesterone levesl in preterm labor.

Progesterone level (nmol/ml)	Group		*p* value *
	P (n=17)	N (n=51)	
Mean (Std Deviasi)	371.25 (224.5)	1201.7 (388.3)	0,001
Median	411.75	1082.54	
Range	62.51-718.25	622.89-2176	

* based on *Mann-Whitney test*

Table 2 showed the level of saliva progesterone in preterm group and normal group. Progesterone level result with ELISA shows preterm group has a lower progesterone level than normal group. This result showed a significant correlation between the level of salivary progesterone and preterm labor with p value < 0.05.

DISCUSSION

Subject characteristics in this study consists maternal age, work and education because they have a possibility as a confounding variable in preterm labor. Age and parity, especially in extreme range, are predisposision factors in preterm labor.[21] Extreme maternal age, 11-18 years and ≥ 35 years are independent factors that can increase preterm labor.[18] Besides, the history of previous preterm labor can increase the risk of recent prterm labor 2.2 times and this risk will increase to 4.9 times if there were three previous preterm labor.[12]

In contrast to the theory, this study showed different result that preterm labor is mainly found at 20-35 years and primipara groups. The incidence of preterm labor will decrease with gestational age and parity.

Occupation as one of the psychosocial factors is known to have an influence to preterm labor. According to theory, preterm labor is lower in a housewive woman than working woman. Physical exhaustion and stress from work can increase the risk of preterm labor. This study revealed that work has no correlation to preterm labor risk based on all the preterm labor studied.[12,13]

Stress in sociodemographic aspect as psychosocial faktors like anxiety, depression, stress, emotional response, social support, behaviour, sexual activity, the desire to get pregnant and demography (maternal age, married status, socioeconomy condition and ethnicity) have a multifactorial role as a stressor. Some studies concluded a correlation between maternal anxiety level, social economy, low education, young age, unmarried status and inadequate prenatal care with the increase of preterm labor risk.[12,13]

This study showed there is a significant correlation between low salivary progesterone level with preterm labor in preterm group. The preterm group has a significant lower progesterone level than normal group (371,25±224.5 versus 1201,7±388,3). This study concluded that the lower the progesterone level, the earlier onset of preterm labor occured. Progesterone is an important hormone during pregnancy that maintains uterine quiscence status.

Progesterone withdrawal has been suggested has a role in inisiation of labor process both of preterm and normal pregnancy. Progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting the production of stimulatory prostaglandins and inhibiting the expression of contraction-associated protein genes within the myometrium. Accumulating evidence suggests that the myometrial activity associated with preterm labor results primarily from a release of the inhibitory effects of pregnancy on the myometrium rather than an active process mediated through the release of uterine stimulants, and progesterone appears to play a central role in this regard. Functional progesterone withdrawal will cause changes in progesterone isoform expression, membrane binding progesterone isoform expression and post-translational modification od progesterone receptor. The change of progesterone receptor mRNA molecule PRA and PRB as well as the increased ratio PRA to PRB will reduce myometrium responsivity to progesterone and enhanced its sensitivity to myometrium contractility process and cervix effacement.[7,14,15,17,18]

Progesterone addition is expected to return the balance of immunology mechanisme in pregnancy. High level progesterone serum will penetrates placenta barrier and increase Th2 domination in maternal and fetal blood circulation throuh Progesterone Induced Blocking Factor (PIBF) so it will inhibit Th1 cytokine synthesis and triggers Th2 cytokine production, followed by enhancement of imunnology humoral response.[9,14]

The American College of Obstetricians and Gynecologists (ACOG) recommends progesterone supplementation especially for women with single pregnancy with previous preterm labor and cervical shortening. Progesterone supplementation suggested pregnant women with cervix length < 1,5 cm in second trimester. Progesterone role in multifetal pregnancy and premature rupture of the membrane needs further study.[14]

CONCLUSION

Salivary progesterone level has a significant correlation with preterm labor.

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