Maternal Urocortin Plasma Level As A Predictor Of Premature Contractions In A Preterm Labor

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Abstract

Background: Preterm labor is alabor occurring in pregnancy with gestational age less than 37 completed weeks (259 days) since the first day of last menstruation period. One of the causes of preterm labor is premature contraction. Urocortin is a neuropeptide in Corticotrophin-Releasing Factor (CRF) family, which binds with CRF receptors. Urocortin will stimulate placenta to release ACTH, which will activate the hypothalamus-hypophysis-adrenal axis and eventually cause contractions. This study aims to evaluate the difference of urocortin levels between mothers experiencing premature contractions compared to normal pregnancy, as well as determining the cut off level of serum urocortin, which may be used as predictor for premature contractions in mothers with preterm labor.

Methods: This was a cross sectional, comparative analytic research. Subjects were women coming to polyclinic or emergency unit of obstetrics and gynecology at Dr. Hasan Sadikin General Hospital or Bandung District General Hospital, whose pregnancy was more than 30 weeks and less than 36 weeks, who had normal pregnancy or experiencing premature contractions, during the period November 2016 to March 2017.

Results: There were total 89 women who participated in this research, 47 (52.8%) were experiencing premature contractions while the other 42 (47.2%) had normal pregnancy. The group of women experiencing premature contractions was found with more risk factors and had higher number of parity compared to women with normal pregnancy. Mean urocortin level in women experiencing premature contractions were higher (5,91 with CI 1,15-10,67) compared to women without premature contractions (0,46 with CI 0,39-0,54) ($P < 0.001$). The cut off point for urocortin level was 0,835(ug/ml) with sensitivity of 97.9% and specificity of 97.6%.

Conclusion: Urocortin level in mothers experiencing premature contractions are higher compared to mothers with normal pregnancy and no premature contractions. Urocortin can be used as predictor for premature labor with cut off point 0.835 ug/ml.

BACKGROUND

Gestational age is an important factor in pregnancy. Term or mature pregnancy last between 37-42 weeks (calculated from the first day of last menstruation period in a regular 28-days cycle). Preterm labor is labor occurring in pregnancy with gestational age less than 37 completed weeks (259 days) since the first day of last menstruation period.[1]

The incidence rate of preterm labor is around 6-15% of all pregnancy. Preterm labor causes 70-75% neonatal morbidity and mortality. Indonesia ranked fifth as the country with the greatest number of preterm labor (15.5%). Prematurity can cause neurological and growth disorders in babies. Prematurity may also cause respiratory disorders (62%), sepsis (28%), interventricular hemorrhage (24%), and pneumonia (20%) in newborn.[1-3]

Preterm labor caused by premature contractions, placenta previa, severe preeclampsia, fetal asphyxia, maternal heart disease, and others. Various factors causing premature contractions include infections or inflammation, activation of hypothalamus-hypophysis-adrenal axis, deciduous bleeding, and pathological uterine stretching. Mature labor is a physiological activation while preterm labor is a pathological process from one or more pathway of labor.[1]

Mechanisms of premature contractions include activation of hypothalamus-hypophysis-adrenal axis. Maturation and activation of this axis will increase fetal cortisol level and

dehydroepiandros teronesulphate (DHEAS). Increased fetal cortisol level will induce the production of corticotrophin releasing hormone (CRH) by the placenta, fetal and deciduous membranes. CRH will stimulate the production of adrenocorticotropine (ACTH) hormone as well as cortisol secretion by maternal and fetal adrenal glands. CRH also cause prostaglandin production to increase by production of prostaglandin synthase and decreased production of prostaglandin dehydrogenase. In the placenta, DHEA/DHEAS is converted into estrogen which will be received by oxytocin receptor in myometrium, eventually increasing uterine contractions. Prostaglandin will cause uterine contractions and cervical effacement as well as increase myometrial sensitivity towards oxytocin.[1,2]

Urocortin is a neuropeptide, belongs to Corticotrophin-Releasing Factor (CRF) family. Urocortin is suspected to bind with CRF receptors. Urocortin will stimulate placenta to release ACTH, which will activate the hypothalamus-hypophysis-adrenal axis. Therefore, urocortin is considered to play an important role in delivery process.[1,2,4]

CRF synthesized by the placenta and chorioamniotic membrane. CRF level in maternal blood increase significantly in the second and third trimester. Serum CRF level is highest during labor and decrease significantly after labor. In preterm labor, serum level CRF in the second trimester is higher compared to other women with similar gestational age.[4]

Urocortin produced by decidual cells (especially syncytiothrophoblasts). Urocortin is one of the specific ligants for CRF receptors. Urocortin is known to be expressed in intrauterine tissues (placenta, fetal and deciduous membrane) during pregnancy. In premature contractions there is an increase of CRF level. CRF receptors may bind to urocortin, therefore it is suspected that there is increased urocortin level during premature contractions.[4] The difference of urocortin levels between pregnancy with premature contractions and normal pregnancy has not been studied. This study aims to evaluate the difference of urocortin levels between mothers experiencing premature contractions compared to normal pregnancy, as well as determining the cut off level of serum urocortin, which may be used as predictor for premature labor in mothers experiencing premature contractions.

METHODS

This research was designed as a cross sectional study, comparative analytic research. Subjects were women coming to polyclinic or emergency unit of obstetrics and gynecology at Dr. Hasan Sadikin General Hospital or Bandung District General Hospital, whose pregnancy was more than 30 weeks and less than 36 weeks, who had normal pregnancy or premature contractions, during the period November 2016 to March 2017. Respondents were recruited consecutively until minimal number of samples was fulfilled. Total respondents included in the research were 89 women.

The inclusion criteria for this research are: (1). Women having normal pregnancy with gestational age more than 30 weeks up to 36 weeks, (2). Women experiencing premature contractions during pregnancy with gestational age more than 30 weeks up to 36 weeks, and (3). Willing to participate in the research after receiving information and signing informed consent forms for the research. Meanwhile, participants will be excluded from the research if: (1). Their blood sample expires or lysis, making laboratory assessment unable to be conducted, (2). Has had inpatient care for premature contractions during the same pregnancy, (3). Has had labor induction during the same pregnancy, (4). Has underwent cerclage during the same pregnancy, and (5). Has received tocolytic medications.

Respondents were asked to affix their signatures on the written informed consent forms before being interviewed to obtain information regarding their age, vital signs, number of previous pregnancy/births, obstetric history, and history of preterm labor, education, marital status, employment, income, body weight and height. Subjects also underwent routine blood test and urocortin assessment.

Data collected underwent two analysis, univariate and bivariate. Numerical variables were analyzed using independent t-test or Mann-Whitney U test, depending on whether the plasma urocortin value was distributed normally. Meanwhile, categorical variables were analyzed using Kolmogorov-Smirnov test. To determine the cut off point for urocortin as predictor for premature labor, a calculation using Receiver Operating Characteristics (ROC) curve was conducted. The inclusion P value was 0.05. Statistical software SPSS version 21.0 was utilized to perform the statistical analyses.

This research had been approved by ethical committee for research at Dr. Hasan Sadikin General Hospital Bandung and affiliated hospitals, as well as Health Research Unit of Faculty of Medicine Universitas Padjadjaran.

RESULTS

There were total 89 women who participated in this research as respondents, 47 (52.8%) were experiencing premature contractions while the other 42 (47.2%) had normal pregnancy. Mean age of women experiencing premature contractions was 28.45 while mean age of women with normal pregnancy was 30. The group of women experiencing premature contractions found with more risk factors and had higher number of parity compared to women with normal pregnancy.

Table 1

Characteristic of Research Subjects

	Premature Contraction (n=47)	Without Premature Contraction (n=42)	P value
Age, mean ± standard deviation	28.45 ± 6.94	30 ± 7.74	0.321
Parity, median (range)	2 (1-7)	2.5 (1-6)	0.103
Age of gestational, median (range)	32 (30-36)	31 (30-35)	0.044
Risk factors, n (%)**			
No risk factor	24 (51.1)	5 (11.9)	
Urinary tract infection	4 (8.5)	-	
Premature rupture of membrane	3 (6.4)	11 (26.2)	
Chronic hypertension	2 (4.3)	9 (21.4)	
Placenta previa	-	10 (23.8)	0.000
Anemia	6 (12.8)	3 (7.1)	
Others (twin pregnancy, IUGR, IUFD, breech presentation, myopia, heart disease, endometriotic cyst, myeloradiculopathy)	8 (17)	4 (9.5)	

Notes:
* Analysis was conducted with Mann-Whiney U as data distribution was abnormal
**For categorical data, homogenization was conducted using Chi-square test or Fisher Exact test if one cell< 5.

Table 2

Comparison of Urocortin Level in Women Experiencing Premature Contractions and Without Premature Contractions

Urocortin level	Range (Median)	Standard Deviation (minimum – maximum)	95% Confidence Interval	p-value
Premature contraction	5.91 (1.23)	16.21 (0.80 – 77.89)	1.15 – 10.67	< 0.001
Without premature contaction	0.46 (0.49)	0.24 (0.02 – 0.84)	0.39 – 0.54	

Notes: P-value was based on Mann-Whitney test

Mean urocortin level in women experiencing premature contractions was higher (5,91 with CI 1,15-10,67) compared to women without premature contractions (0,46 with CI 0,39-0,54) (P<0.001). There was a significant correlation between the two groups with urocortin level.
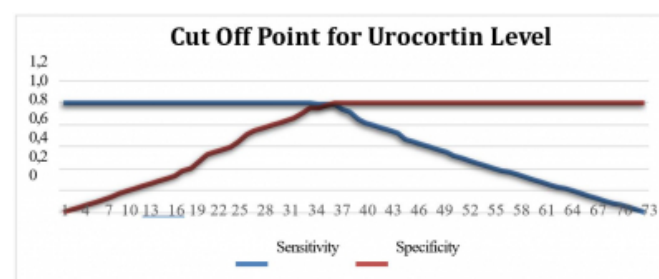
Figure 1

ROC Curve of Urocortin Level in Research Subjects
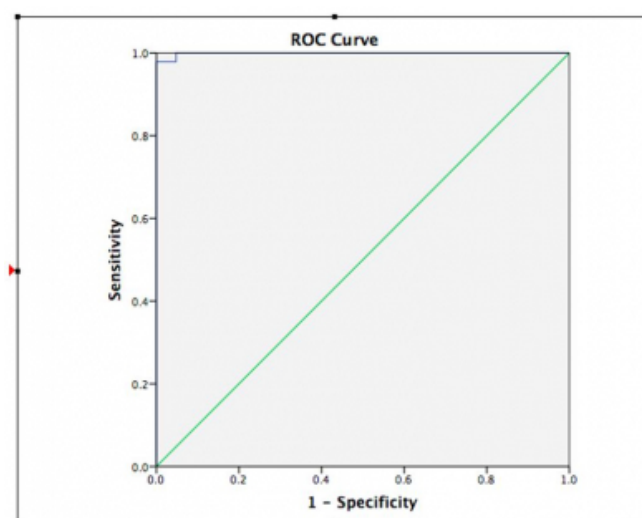
Urocortin level has a good diagnostic value since the curve was far from the 50% line and nearing the 100% line. Area under curve (AUC) points obtained from ROC (Receiver Operating Characteristic Curve) method was 99.9% with 95% (CI 99.6%-100%), p<0.001.

Figure 2

Cut off Point for Urocortin Level in Research Subjects

Sensitivity and specificity curve was shown with a cut off point as the optimal score of the two indicators. The optimal cut off point was between the 33 and 35 mark, which was 34. The cut off point had the value of 0,835(ug/ml) with sensitivity of 97.9% and specificity of 97.6%.

DISCUSSION

There were total of 89 respondents in this research, 47 (52.8%) were experiencing premature contractions while the other 42 (47.2%) had normal pregnancy. The two research groups were compared by age, number of previous births, gestational age, and risk factors for premature contractions.

Distribution of research subjects based on age and parity had p-score >0.05. Women experiencing premature contractions had younger mean age and lower total parity compared to

women with normal pregnancy. In the year 2007, Toricelli et al conducted a research between groups of term and preterm labors based on maternal plasma urocortin level. It found that mean age of women in term labor group was higher (28.7) compared to women in preterm labor group (28.6). Meanwhile, based on parity, Toricelli et al found that women in term labor group had lower parity compared to women in preterm labor group.5

In this research, the distribution of research subjects based on gestational age was analyzed using Mann-Whitney U test as the distribution was abnormal. Mean gestational age in women experiencing premature contractions was higher compared to women without premature contractions. Toricelli et al evaluated clinical and demographic characteristics of their research subjects and found similar mean gestational age between women having premature labor and women experiencing premature contractions in this research (32weeks).5

Distribution of research subjects based on risk factors was analyzed using Chi-square test. It was shown that women with more risk factors tended to experiencing premature contractions.

In this research, maternal blood plasma obtained from group of women experiencing premature contractions and women without premature contractions. Blood samples were chosen as the method of sample collection as it was a non-invasive procedure. A research by Toricellietal in Italy and United Kingdom described that plasma urocortin maybe used as predictor for preterm labor.5

In this research, mean urocortin level in women experiencing premature contractions was higher compared to women without premature contractions. Mean urocortin level in women experiencing premature contractions was 5.91 ug/ml (CI 1.15-10.67) while in women without premature contractions was 0.46 pg/ml (CI0,39-0,54)(p<0,001).

In a few previous researches, pregnant women who experienced preterm labor had increased urocortin level in maternal plasma compared to women with normal pregnancy. Toricelli et al conducted a research on urocortin level in groups of women who delivered their babies in 7 days or less after arriving at hospital and women who delivered their babies in more than 7 days after arriving at hospital and experiencing premature contractions. The results showed that maternal plasma urocortin concentration

was significantly higher (p<0.0001) in women who had preterm labor compared to women who had term labor.6 Increased maternal plasma urocortin level was related to preterm labor and this result was supported by in vitro researches which found that urocortin induce myometrial contractility, which arose a suspicion that increased urocortin level in maternal circulation is related to impending preterm labor.6-8

Based on the data collected in this research, a table was constructed based on urocortin level, starting from urocortin level with high sensitivity and low specificity score up to urocortin level with low sensitivity and high specificity score. Cut off point for urocortin level which can be used as predictor for premature contractions was calculated using Receiver Operating Characteristics (ROC) curve. The ROC curve resulted in cut off point of 0.835 ug/ml with sensitivity of 97.9% and specificity of 97.6%. This meant that pregnant women with urocortin level >0.835 ug/ml had risks for having preterm labor.

Similar research was done by Toricelli et al in the year 2005 and 2007. They reported that maternal plasma urocortin concentration was significantly higher (p<0.0001) in women having premature labor (median 131.2 pg/ml, CI 115.1-139.4 pg/ml) compared to women having mature labor (95.4 pg/ml, CI 69) With sensitivity of 80% [95% CI 61.4-92.2%] and sensitivity of 100% [95% CI 93.4-100%] as indicator markers for preterm labor incidence. The research was conducted in a few ethnics group. The research also described various differences in plasma urocortin level between white and black people in the term labor group (ratio 47:3) and in preterm labor group (ratio 25:2).6

The author wishes that the result of this research can be used as a reference to detect impending preterm labor in order to decrease the morbidity and mortality of babies who were born prematurely.

CONCLUSION

Urocortin level in mothers experiencing premature contractions are higher compared to mothers with normal pregnancy and no premature contractions. Urocortin can be used as predictor for premature labor with cut off point 0.835 ug/ml.

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