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RESEARCH

Diagnostic Value of Cyclooxygenase-2 Serum Levels in Predicting Preterm Labor

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Abstract

Objective: To determine the value of serum cyclooxygenase 2 in predicting preterm labor

Method: Examination of serum COX-2 levels by ELISA method in pregnant women with 28 weeks to 36 weeks of pregnancy compared with pregnant women with ≥ 37 weeks of gestation at the time of first stage of active phase

Results: It is known that the average COX-2 level in preterm labor is 21.88 ± 18.22 higher than in term labor which is 4.88 ± 2.35 ng / ml, the statistical test results obtained $p = < 0.001$ serum Cyclooxygenase 2 at preterm deliveries and term deliveries. The value of serum cyclooxygenase 2 levels in predicting preterm labor is at a cut point of 7.0.0 ng / ml with a sensitivity of 86.1% and a specificity of 86.1%

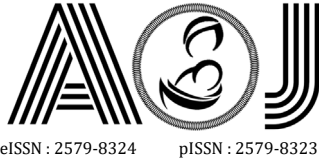
Conclusion: There were significant differences in serum cyclooxygenase 2 levels in preterm labor and term delivery

Keywords: cyclooxygenase 2, memprediksi persalinan preterm, persalinan preterm.

INTRODUCTION

Preterm labor is a cause of perinatal morbidity and mortality worldwide. Preterm labor causes 70% perinatal and neonatal mortality, and long-term morbidity, which includes mental retardation, cerebral palsy, developmental disorders, seizure disorders, blindness, hearing loss, and non neurological disorders, such as chronic lung disease and neuropathy. WHO defines preterm labor as labor at less than 37 weeks' gestation or less than 259 days, counting from the first day of the last menstrual cycle, or with a birth weight less than 2500 g^{1,2}.

Seventy percent of the incidence of preterm labor with a gestational age of less than 30 weeks is related to intrauterine infection, compared with gestational age of more than 30 weeks (30-40%). In preterm labor, labor is triggered before term. Triggers for these pathological conditions include intra-uterine infection, uterine over distention, uteroplacental ischemia, cervical abnormalities and other things that cannot be explained. Of the several triggers above intra uterine infection causes 40% of preterm labor³. The mechanism of preterm labor induced by infection is basically an inflammatory reaction that is influenced by maternal and fetal factors. Bacterial invasion will produce bacterial products



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in the form of phospholipase A2 (PLA2), endotoxin and collagenase. The product will stimulate a cytokine cascade characterized by the formation of interleukin-1 (IL-1), tumor necrosing factor (TNF), interleukin-6 (IL-6), interleukin-8 (IL-8) by macrophages and inflammatory cells decidua activated.³

PLA2 will induce glycerophospholipids from cell membranes and then turn into arachidonic acid and subsequently produce cytokine cascades to produce prostaglandin E2 (PGE2) through the COX - 2 pathway. Actually arachidonic acid produced by that process. It will be partly converted through the lipoxygenase pathway into leukotrienes (LT) and 5-hydroxycoisatetraenoic acid (5-HETE) and then stimulates uterine contractions⁴.

METHOD

The study was an observational analytic study with a cross sectional comparative study approach. This study was conducted on all patients who experienced preterm labor at the first active phase and gestational age between 28 (+ 0 days) week and 36 (+ 6 days) weeks which were assessed based on the last menstrual period (LMP) and or patients who had already on USG from the 1st trimester of pregnancy during 2019. It carried out in the Obstetrics and Gynecology Section / SMF of Network Hospital, Community Health Center, General Central Hospital of Dr. M. Djamil Padang and at the Biomedical Laboratory, Faculty of Medicine, Univesitas Andalas, Padang. The controls were women who had term deliveries (≥ 37 weeks) during the first active phase who were treated in the Obstetrics and Gynecology Section of the Network Hospital, the Network Health Center and the Central General Hospital of Dr. M. Djamil Padang. Sampling in research is by Consecutive Sampling. Samples were examined for COX-2 serum levels by the ELISA method.

RESULT

The research subjects consisted of 72 respondents, of which 36 respondents with preterm labor and 36 respondents with term labor at the active phase

Data Normality

Data normality test results can be seen in Table 1. below:

Table 1. Data Normality Test

COX-2	n	Mean \pm SD	p value
Preterm labor	36	21,88 \pm 18,22	0,057
Term Labor	36	4,88 \pm 2,35	0,069

Based on table 1 it is known that the results of the normality test of COX-2 levels of respondents in preterm and term delivery were normally distributed ($p > 0.05$).

Characteristics of Respondents

Table 2. Characteristics of Respondents by Age

Variabel	Preterm (Mean \pm SD)	Term (Mean \pm SD)	p-value
Age (years)	29.03 \pm 4.76	30.03 \pm 4.60	0.368
Parity	1.64 \pm 1.39	1.47 \pm 1.25	0.596
Body mass index (kg / m ²)	21.52 \pm 1.34	22.09 \pm 1.97	0.154
Leukocytes	12.715,83 \pm 1.132,13	11.000,00 \pm 1.293,94	0.001

Based on Table 2. there were no differences in the mean age, parity and body mass index of respondents in preterm and term delivery ($p > 0.05$). However, there were differences in leukocyte levels in preterm and term labor ($p < 0.05$).

Differences in Serum Cyclooxygenase 2 Levels in Preterm Labor and Aterm Labor

Table 3. Differences in Levels of Serum Cyclooxygenase 2 in Preterm and Term Labor

COX-2	n	Mean \pm SD	p- value
Preterm Labor (ng / ml)	36	21.88 \pm 18.22	<0.001
Term Labor (ng / ml)	36	4.88 \pm 2.35	

Based on Table 3 the mean of COX-2 levels in preterm labor are higher than term labor. The statistical test results obtained p value <0.001, it can be concluded that there are significant differences in serum cyclooxygenase 2 levels in preterm labor and term labor.

Diagnostic Value of Cyclooxygenase 2 Serum Levels in Predicting Preterm Labor

The diagnostic value of serum cyclooxygenase 2 levels in predicting preterm labor can be done through Receiver Operating Characteristic (ROC) analysis, shown in Figure 1

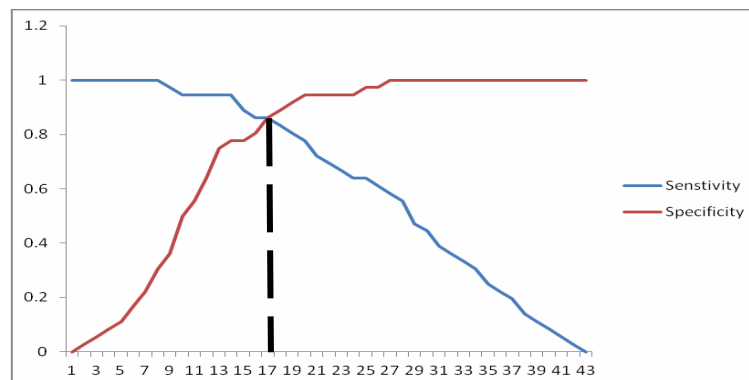


Figure 1. Sensitivity and Specificity Based on Cut-Off Points According to ROC (Receiver Operating Characteristic) Analysis

From Figure 1. it is known that the optimal cut point at the intersection of the sensitivity and specificity line is point 17. The diagnostic value of serum cyclooxygenase 2 levels in predicting preterm labor at cut-off point 17 is 7.039 ng / ml whose sensitivity value is 86.1% and the specificity is 86.1%. The accuracy of serum cyclooxygenase 2 levels in predicting preterm labor can be seen in the following figure 2.

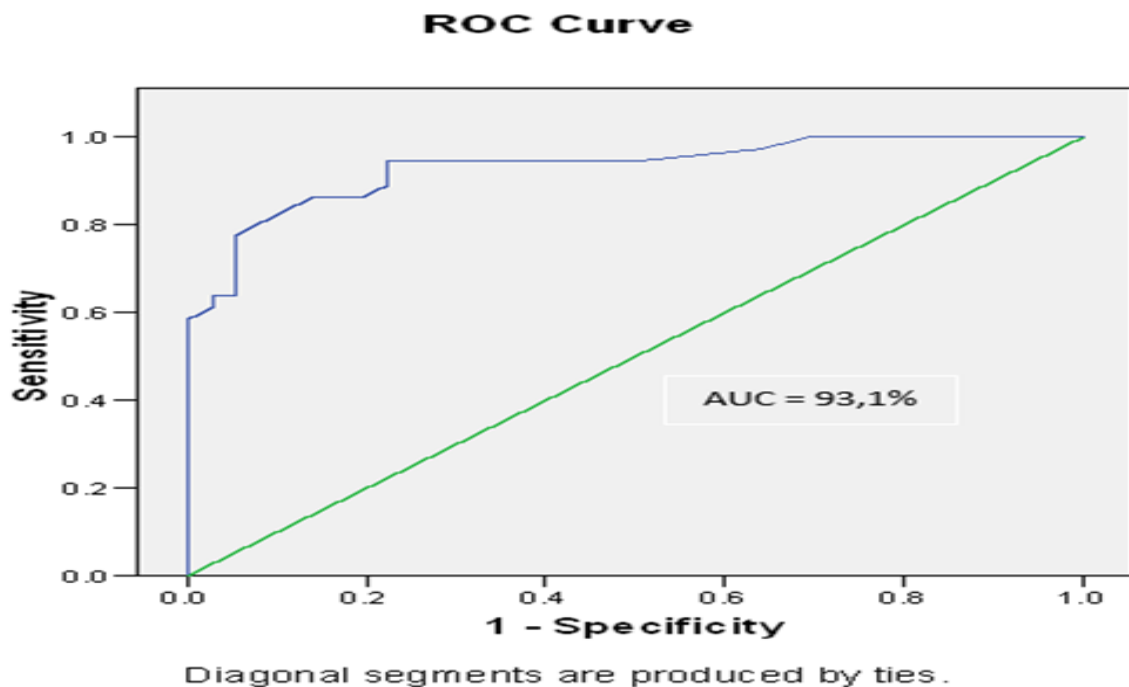


Figure 2. Accuracy of Cyclooxygenase 2 Serum Levels in Predicting Preterm Labor

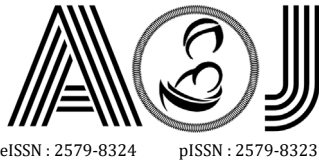
Based on Figure 2, the value of area under the curve (AUC) in the ROC analysis was 93.1%, it can be concluded that the accuracy of cyclooxygenase 2 serum levels in predicting preterm labor is very good accuracy category.

DISCUSSION

Differences in Serum Cyclooxygenase 2 Levels in Preterm Labor and Term Labor

The statistical test results obtained p value <0.001, it can be concluded that there are significant differences in serum cyclooxygenase 2 levels in preterm labor and term labor. These results are in line with previous studies conducted by Loudon (2003) where there were differences in COX-2 levels in preterm and term labor. The level of COX-2 in preterm labor was 16.13 ± 4.71 ng / ml higher than in term labor 10.11 ± 5.69 ng / ml. Stating the average COX-2 in preterm labor was 88.75% compared to 46% in normal labor.

Another study conducted by Djanas (2018) found that COX-2 levels were higher in preterm labor which was 11.02 ± 3.33 ng / ml compared to term delivery at 8.77 ± 1.36 ng /



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ml, the statistical test results obtained $p = 0.012$ (p value < 0.05) then there are differences in COX-2 levels between preterm labor and term delivery.

Based on the theory there is a relationship between preterm labor and subclinical inflammatory response in maternal or fetal tissue. Seventy percent of the incidence of preterm labor with a gestational age of less than 30 weeks is associated with intrauterine infection. Infection is an important disease mechanism in preterm labor.

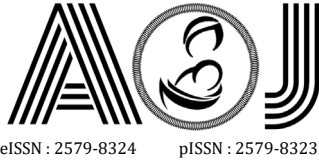
This infection process is followed by an inflammatory response which includes the secretion of cytokines / chemokines by the body and infiltration of immune cells into the reproductive tissues and the fetus / mother. Pro-inflammatory cytokines stimulate the production of matrix metalloproteinases (MMP) -2, -8, -9, COX-2, collagenases and prostaglandins which cause cervical softening and rupture of the membranes. TNF- α and IL- β increase contractility whereas COX-2, PGE-2, IL-6 regulates OT receptors in myometrial cells that play a role in myometrial contractility⁵.

Infection triggers proinflammatory cytokine stimulation, namely TNF- α , which plays a role in the activation of Nuclear Factor Kappa Beta (NF- κ B) and COX-2. The presence of proinflammatory cytokines has an effect on cell membrane phospholipids altered by phospholipase A2 and will increase arachidonic acid and form prostaglandins by activation of high COX-2. Increased COX-2 also affects the functional withdrawal of progesterone through the interaction of progesterone receptors thereby increasing prostaglandin levels⁶. Increased prostaglandin levels cause activation of the enzyme collagenase, blood vessel dilatation and uterine contractions⁷. Activation of amnion cytokines, decidua and chorion will increase apoptosis, through the process of amniotic membrane damage, reduction in cell density and degradation of the extracellular matrix which triggers thinning of the membranes causing rupture of membranes⁸. This explains that the combination of cervical dilatation, uterine contractions and rupture of membranes can cause premature labor⁹.

Researcher's analysis found that differences in COX-2 levels in preterm labor were higher than in term labor due to inflammation that occurs in preterm labor, activating proinflammatory cytokines that can stimulate myometrial contraction through increased synthesis of TNF- α which increases COX-2 levels so that in the end, it will increase prostaglandin levels, prostaglandins will further increase intracellular calcium uptake so that calcium levels that can be used by the myometrium increase and then will cause contractions. Conditions of contraction triggers preterm labor.

Diagnostic Value of Cyclooxygenase 2 Serum Levels in Predicting Preterm Labor

Based on the result, it can be concluded that the accuracy of cyclooxygenase 2 serum levels in predicting preterm labor is very good accuracy category. The research stated that COX-2 may be a predictor in determining the occurrence of preterm labor, an increase of COX-2 in



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86% of labor may determine the risk of preterm labor¹⁰. Meta-analysis stated that the discovery of the effect of COX to the occurrence of preterm labor, it is necessary to treat with COX-2 inhibitors for the prevention and treatment of preterm labor¹¹.

Progesterone and COX-2 markers as a determinant of success in the prevention of preterm labor. They form a computer simulation with linear equations to predict the risk of preterm labor, which is expected that application can prevent preterm labor and prevent high-cost treatment¹².

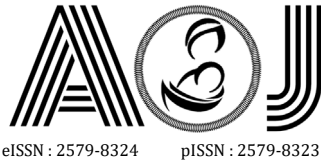
Preterm labor begins with high levels of prostaglandins in the amniotic fluid. Prostaglandins (PG) are able to soften the cervix by increasing proteoglycans and changing the biophysical properties of collagen^{7,8}. Prostaglandins are a form of prostanoids. Prostanoid production at the site of injury is a major component of the inflammatory reaction. Prostanoids are formed by arachidonic acid which is from phospholipid membranes, with the help of phospholipase-A2, Cyclooxygenase-2 (COX-2) can convert arachidonic acid into prostaglandin H, then convert it to specific prostanoid species, for example prostaglandin E₂⁶. COX2 is triggered by IL-1 and TNF- α , both of them were formed a few hours after the onset of inflammation. Increasing of endometrial COX-2 and prostaglandins, and uterine contractions causing ischemia and pain.

Excessive secretion from inflammatory cytokines as occurs in amniotic infections causes adverse effects on intra-uterine tissue such as abortion and preterm labor. The absence of proinflammatory cytokines, such as COX-2, is expected to play an important role in preterm labor and term labor by changing the status of the uterus from rest to an active state^{6,7}.

Based on the analysis of researchers in the case of preterm labor, COX-2 plays a role in stimulating uterine activity and cervical maturation process by producing prostaglandins, cortisol and degrading extracellular matrix from the amniotic membrane. In preterm labor, COX-2 levels increased. Therefore, It is necessary to use COX-2 levels as a predictor in predicting preterm labor by utilizing the diagnostic value found by researchers.

CONCLUSION

There are significant differences in serum levels of cyclooxygenase 2 in preterm labor and term labor. The diagnostic value of Cyclooxygenase 2 serum levels in predicting preterm labor is at a cutoff point of 7.039 ng / ml with sensitivity value is 86.1%, specificity value is 86.1%, and accuracy is 93.1



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