

Research Article

Maternal Serum Interleukin-6 Level in Correlation with Preterm Delivery

Hubungan Kadar Interleukin-6 Serum Maternal dengan Persalinan Preterm

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Abstract

Objective: To determine the correlation between maternal serum Interleukin-6 (IL-6) serum level with preterm delivery.

Methods: We performed an observational cross-sectional study of 30 pregnant women between 21 to 36 week gestational age with and without labour (delivery) in Prof. Dr. RD. Kandou Hospital Manado. Samples were collected with consecutive sampling method. Data was analyzed using Mann-Whitney test with significance level of $p < 0.05$.

Results: We encountered 15 preterm pregnancy and 15 preterm delivery, 6 (40%) cases belonged to the age group < 20 years old. Incidence of preterm delivery with history of preterm delivery in a previous pregnancy was 6 cases (40%). This study found that the mean maternal serum IL-6 level in preterm delivery was 12.9 pg/ml, which was higher than preterm pregnancy (2.14 pg/ml).

Conclusion: There is significant correlation between maternal IL-6 serum level with preterm delivery which was higher at 4.55-38.87 pg/ml than women with preterm pregnancy (1.5-3.07 pg/ml).

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Keywords: Interleukin-6 level, maternal serum, preterm delivery, preterm pregnancy

Abstrak

Tujuan: Mengetahui hubungan antara kadar Interleukin-6 (IL-6) serum maternal dengan persalinan preterm.

Metode: Penelitian ini merupakan studi potong lintang observasi yang mengikutsertakan 15 perempuan hamil dengan persalinan preterm dan 15 perempuan dengan kehamilan preterm, dengan usia kehamilan 21-36 minggu yang datang ke bagian kebidanan dan kandungan RSUP Prof. Dr. RD. Kandou Manado. Sampel dikumpulkan melalui metode consecutive sampling. Seluruh pasien terlibat dalam penelitian ini secara sukarela yang dinyatakan dengan informed consent. Analisis data menggunakan uji Mann-Whitney test dengan tingkat kemaknaan $p < 0,05$.

Hasil: Didapatkan persalinan preterm terbanyak pada kelompok usia < 20 tahun dengan 6 kasus (40%), dan angka kejadian persalinan preterm pada riwayat persalinan preterm pada kehamilan sebelumnya didapatkan 6 kasus (40%). Pada penelitian ini didapatkan rata-rata kadar IL-6 serum maternal pada persalinan preterm (12,9 pg/ml) lebih tinggi jika dibandingkan dengan kehamilan preterm (2,14 pg/ml).

Kesimpulan: Terdapat hubungan bermakna antara kadar IL-6 serum maternal dengan persalinan preterm, di mana pada kelompok persalinan preterm lebih tinggi, yaitu 4,55 - 38,87 pg/ml, dibandingkan pada perempuan hamil dengan kehamilan preterm yaitu 1,5 - 3,07 pg/ml.

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Kata kunci: kadar Interleukin-6, kehamilan preterm, persalinan preterm, serum maternal

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INTRODUCTION

Preterm delivery is still a serious problem until now, with preterm labor still occurring in $> 12\%$ of pregnancies. In the United States, there is 1 incidence of preterm labor for 8 normal labors. Preterm delivery occurred approximately in 10% of all pregnancies per year worldwide and constitutes a major cause of morbidity and perinatal mortality. More than half of the infants who survive, experience long term morbidities.¹⁻³ The incidence of preterm labor in Prof. Dr. RD. Kandou Hospital, Manado in the period of January 1, 2012 until December 31, 2012 was 15.5%, accompanied by 44 cases of perinatal mortality, of which 57.39% was

caused by respiratory distress syndrome. Based on the statistical data in 2011, the infant mortality rate in North Sulawesi amounted to approximately 33 per 1,000 live births. Most of the infant mortality rate (45-55%) was attributed to preterm labor.⁴⁻⁶

A simple, rapid, non-invasive, and safe marker examination related with the occurrence of preterm birth and neonatal respiratory morbidity may be useful both in the development of risk stratification strategies and morbidity prediction in pregnant women who will experience preterm labor; or in developing safe and efficient drugs that works selectively against uterine contraction to prevent preterm labor. This surely will provide significant

impact on early intervention, either in the prevention or treatment of preterm labor.

Cytokines may be a promising marker as the early phase mediators of an inflammatory response. IL-6 is a proinflammatory cytokine that is a useful marker in indicating the presence of intrauterine infection, preterm labor and neonatal morbidity.^{7,8}

Several studies have consistently demonstrated an association between elevated levels of serum IL-6 in the fetal and/or neonatal 'compartment' (such as amniotic fluid, umbilical vein, fetal blood, neonatal blood) with preterm labor and/or neonatal morbidity.⁹⁻¹² However, data consistency is still lacking in the analysis of relationship between level of maternal serum IL-6 with the occurrence of preterm birth. IL-6 is a more promising examination than other methods of maternal serum screening. Several studies have shown that maternal serum IL-6 level is also elevated in intrauterine infection, either clinically evident or those only proven in histologic findings. Thus, the finding of increased IL-6 is not only observed in amniotic fluid, cervicovaginal secretions, umbilical vein, and fetal blood, but also in the serum of women with intrauterine infections, both clinically and subclinically.^{8,13,17} On the other hand, other studies have shown an inconsistent relationship between maternal serum IL-6 level and preterm labor.

However, recent research conducted by Yoram Sorokin et al (2010) suggested a relationship between maternal serum IL-6 level with the occurrence of preterm birth and neonatal morbidity. In this sense, IL-6 can be a useful marker for intrauterine infection, preterm birth and neonatal morbidity. IL-6, a proinflammatory cytokine, is a major mediator of inflammatory response and infection; and an early marker of acute phase response.¹⁴

Based on the findings above, this study was conducted to determine whether there is relationship between level of maternal serum IL-6 with the occurrence of preterm birth.

METHODS

This study was an analytic cross-sectional study conducted in the department of Prof. Dr. RD. Kandou Hospital, Manado. It was conducted from December 2013 until the required sample size was met.

The study sample consisted of women with preterm labor and women with preterm pregnancies who presented to the delivery room of the Department of Obstetrics and Gynecology, Prof. Dr. RD. Kandou Hospital and RW. Monginsidi Hospital that met the inclusion and exclusion criteria. The sampling method used was consecutive random sampling with maternal serum IL-6 as the study variable. Examination of serum IL-6 was conducted in Prodia Laboratory. Three cc of peripheral venous blood samples were withdrawn and put into an SST test tube, which were then sent to Prodia Laboratory Manado to be centrifuged. The sample would then be sent to the Prodia in Jakarta for examination of serum IL-6 level using Quantikine ELISA KIT D6050.

Inclusion criteria in this study included pregnant women with a single live fetus, intrauterine, 21-36 weeks gestational age who experienced preterm labor with <2500gr baby as the case group; and pregnant women with a single fetus, live, intrauterine, 21-36 weeks gestational age that was not in labor with the estimated fetal weight <2500gr as the control group. Patients were recruited from the outpatient clinic and delivery room of the Obstetrics and Gynecology department of Malalayang Hospital, RW. Monginsidi Hospital. All the samples were willing to participate in the study voluntarily, which was expressed by informed consent. Exclusion criteria included women who had a history of diabetes, hypertension, heart, kidney and liver disease, pneumonia, tuberculosis, malaria, hepatitis, typhoid, multiple pregnancy, polyhydramnion, premature rupture of membranes, fetal congenital abnormalities as well as patients who were not willing to be recruited in the study.

RESULTS

From Table 1, we can observe the age group distribution of our samples in the study and control group.

Table 1. Characteristics of Sample by Age

| Maternal age | Labor status | | | |
|-----------------------|---------------|------|-------------------|-----|
| | Preterm labor | | Preterm Pregnancy | |
| | N | % | N | % |
| <20 years, ≥ 35 years | 7 | 46.7 | 3 | 20 |
| 20 - 34 years | 8 | 53.3 | 12 | 80 |
| Total | 15 | 100 | 15 | 100 |
| x ² | p = 0.121 | | | |

As can be seen in Table 2, based on maternal parity, the highest number of preterm labor incidence occurred in primigravidae (60%).

Table 2. Characteristics of Sample by Parity

| Parity | Labor status | | | |
|----------------|---------------|-----|-------------------|------|
| | Preterm labor | | Preterm Pregnancy | |
| | N | % | N | % |
| Primigravida | 9 | 60 | 5 | 33.3 |
| Multigravida | 6 | 40 | 10 | 66.7 |
| Total | 15 | 100 | 15 | 100 |
| x ² | p = 0.143 | | | |

In Table 3, characteristic was based on history of preterm delivery. We can observe that the incidence of previous preterm labor in the preterm labor group was as much as 40%, whereas the incidence in preterm pregnancies (controls) only amounted to 7%.

Table 3. Characteristics of Sample based on History of Preterm Labor

| History of preterm labor | Labor status | | | |
|--------------------------|---------------|-----|-------------------|-----|
| | Preterm labor | | Preterm Pregnancy | |
| | N | % | N | % |
| Yes | 6 | 40 | 1 | 7 |
| No | 9 | 60 | 14 | 93 |
| Total | 15 | 100 | 15 | 100 |
| x ² | p = 0.031 | | | |

In Table 4, we can observe the difference in maternal serum IL-6 level found in both groups was statistically significant (p = 0.001).

Table 4. Levels of Maternal Serum IL-6 in Preterm Labor Group and Preterm Pregnancy Group

| IL-6 value | Labor status | |
|----------------------|---------------|-------------------|
| | Preterm labor | Preterm Pregnancy |
| Average IL-6 (pg/ml) | 2.14 | 0.511 |
| SD (pg/ml) | 12.89 | 8.800 |
| Mann-Whitney | p = 0.001 | |

DISCUSSION

Based on the age characteristics, the highest number of cases was observed in the <20 years age group, as much as 6 cases (40%). This was similar to the research conducted by Peacock et al (1995) and Creasy et al (2004), which stated that the incidence of preterm delivery were mostly obtained in women whose age were too young.^{15,16} However, in this study, the statistical analysis showed no significant relationship between maternal age with the incidence of preterm labor. These results were in contrast to several studies that reported a significant association between young maternal age with preterm labor. This may be caused by the small sample size, causing random errors affecting the results of statistical tests on groups of very young maternal age.

In Table 2, based on the characteristics of parity group, the highest number was found in the primigravida group of preterm labor (60%). However, the results of statistical tests in this study showed no significant relationship between parity and the incidence of preterm labor (p=0.143).

In Table 3, based on the characteristics of previous history of preterm delivery, the incidence of preterm delivery in patients with a history of preterm labor in a past pregnancy was as much as 40%. These results were similar to the research conducted by Pennel et al (2007), which stated that women who had experienced preterm labor had a risk of experiencing preterm delivery in subsequent pregnancies by 15%.¹⁶ The incidence of recurrent preterm labor can be caused by genetics, which is in line with research conducted by Hoffman and Ward (1999), which suggested that genetic factors play a role in the etiology of preterm

labor. Genes that regulate decidual relaxin is one of the cause. From the results of statistical tests, there was also a significant association between history of preterm labor with the incidence of preterm labor ($p=0.031$). Furthermore, research conducted by Goldenberg et al (2000) found a significant relationship between history of preterm labor with the occurrence of preterm delivery in subsequent pregnancies.¹⁷

This study found that serum maternal IL-6 level in preterm labor was 4.55 pg/ml to 38.87 pg/ml, whereas in preterm pregnancies the result obtained was 1.5 pg/ml to 3.07 pg/ml. In this study, it was found that the average level of serum maternal IL-6 was higher in preterm labor, which was 12.9 (SD=9.95) pg/ml compared with preterm gestation, which was 2.14 (SD=0.511) pg/ml. This result supported results of previous studies. Phillip et al (1997) found significant differences in the average level of serum maternal IL-6 between groups of preterm labor with preterm pregnancies (9.3 pg/ml vs. 1.9 pg/ml, $p<0.001$). This study found that improvement in maternal serum IL-6 may be a sign of impending preterm delivery in patients with and without subclinical intrauterine infection.¹⁸ Moreover, Snjezana et al (2007) found that the level of maternal IL-6 serum was significantly higher in patients with preterm labor compared to patients with preterm pregnancies (6.8 pg/ml vs. 21.9 pg/ml, $p<0.05$).¹⁹ Vogel et al (2007) evaluated levels of 17 inflammatory markers including IL-6 in 69 samples of preterm maternal serum, and obtained results that high level of maternal IL-6 serum was associated with increased risk of preterm labor at less than 35 weeks of gestational age.²⁰ Likewise, this study is similar with a study conducted by Yoram Sorokin et al (2010) at Wayne State University, who suggested a relationship between level of maternal serum IL-6 with the occurrence of preterm birth and neonatal morbidity.

IL-6 is a useful marker for intrauterine infection, preterm delivery, and neonatal morbidity. Increased level of maternal IL-6 serum is a risk factor for the occurrence of preterm labor. In the study by Yoram Sorokin, it was stated that the concentration of IL-6 of more than 5.15 pg/ml can lead to an increased risk of preterm labor by 38.30% ($p<0.005$).¹⁴ Recent research conducted by Ramsey et al in 2011, obtained a significant association between IL-6 level with the onset of labor, where it

was said that the average IL-6 level was significantly higher in pregnant women undergoing labor at term compared with full-term pregnant women who were not in labor yet (2.05 pg/ml vs. 0.95 pg/ml, $p=0.03$).²⁰

CONCLUSIONS

In this study, level of maternal serum IL-6 in the preterm pregnancy group was 1.5 pg/ml to 3.07 pg/ml, and in the preterm labor group was 4.55 pg/ml to 38.87 pg/ml. Statistically, level of maternal serum IL-6 was significantly much higher in the preterm labor group ($P=0.001$). IL-6 level was correlated with the incidence of preterm labor. We suggest that a larger study with more samples be performed in order to determine the cut off point, so that level of maternal serum IL-6 can be used as a supporting tool to predict the onset of preterm labor.

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