Research Article

Elevated Serum Ferritin and Interleukin-6 Level are Risk Factors for Preterm Labour

Kadar Feritin dan Interleukin-6 Serum yang Tinggi Merupakan Faktor Risiko Terjadinya Persalinan Preterm

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Abstract

Objective : To investigate the association of serum ferritin and Interleukin-6 (IL-6) elevation as the risk factors for preterm labor.

Methods : This study was a case-control study conducted at the Obstetrics and Gynecology Outpatient and Emergency Department at Sanglah General Hospital Denpasar, Bali in November 2014 until June 2015. The sample selection was done by consecutive sampling with total sample as many as 20 case samples (women with preterm labor) and 20 control samples (women with normal preterm pregnancy).

Results : Based on the analysis, there was no significant difference of patient demografic such as age, gestational age, and parity among the two groups. Chi-square analysis showed that the increased serum ferritin level had 5 fold increased risk of developing preterm labor (OR = 4.89, 95% CI = 1.20-19.94; p = 0.022), and increased serum IL-6 level had 9 fold increased risk of developing preterm labor (OR = 9.33, 95% CI = 2.18-39.96; p = 0.001) compared to normal preterm pregnancy.

Conclusions : It can be concluded that level of IL-6 and serum ferritin was the risk factor for preterm labor.

Keywords : Interleukin-6, preterm labor, serum ferritin

Abstrak

Tujuan : Untuk membuktikan hubungan kadar feritin dan Interleukin-6 (IL-6) serum yang tinggi sebagai faktor risiko terjadinya persalinan preterm.

Metode : Penelitian ini bersifat observasional dengan studi case-control yang dilakukan di Poliklinik dan IGD Kebidanan dan Penyakit Kandungan RSUP Sanglah Denpasar, yang dilakukan mulai bulan November 2014 hingga Juni 2015. Pemilihan sampel dilakukan dengan cara berurutan dengan sampel penelitian sebanyak 20 sampel kasus (ibu dengan persalinan preterm) dan 20 sampel kontrol (ibu hamil preterm normal).

Hasil : Tidak didapatkan perbedaan bermakna dari demografik pasien yaitu usia, usia kehamilan, dan paritas pada kedua kelompok. Analisa chi-square menunjukkan peningkatan kadar feritin serum memiliki peningkatan risiko 5 kali terjadinya persalinan preterm (OR = 4,90, IK 95% = 1,20-19,94; p = 0,022), dan peningkatan kadar IL-6 serum memiliki peningkatan risiko 9 kali terjadinya persalinan preterm (OR = 9,33, IK 95% = 2,18-39,96; p = 0,001) dibandingkan dengan kelompok ibu hamil preterm normal.

Kesimpulan : Kadar feritin dan IL-6 serum adalah faktor risiko terjadinya persalinan preterm.

Kata kunci : feritin serum, interleukin-6, persalinan preterm.

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INTRODUCTION

Preterm labor causes complication towards the neonates due to the immaturity of the preterm babies, such as respiratory distress syndrome, anemia and retinopathy of prematurity, and systemic infection.[1] This correlates with the high number of Neonatal Mortality Rate in Indonesia which was 19 out of 1000 live births based on Survei Demografi dan Kesehatan Indonesia (SDKI).[2] The mortality and morbidity of preterm babies are relatively high despite the intensive care for neonates have been improved throughout the world. Early detection towards preterm labor is one of prevention that can be conducted, by detecting risk factor, evaluating cervical length, fetal fibronectin and also measuring biological and genetical marker.[3]

Various etiology of preterm labor have been identified, which one of them is the infection by the entrance of microorganism towards maternal body that initiates the inflammation cascade and increase the inflammation cytokines. This cascade will increase the level of prostaglandin and metalloproteinase that triggers the preterm labor.[4,5] Infection or inflammation will increase Interleukin-1 (IL-1) as the primary mediator, that initiates the other interleukin such as Interleukin-6 (IL-6), and also increase the translation of ferritin.[6] By evaluating the serum ferritin and IL-6 level as the inflammatory biomarker,the result from this study was designed to improve the early detection method towards preterm labor, that can prevent and decrease the preterm labor and also neonatal mortality rate.

METHODS

A case-control study was performed. The inclusion criteria for the case samples was pregnant women with preterm labor, while the control samples were pregnant women in preterm gestational age without sign of labor. Both group was evaluated for the serum ferritin and and IL-6 by obtaining venous blood. The exclusion criteria for both group were pregnancy with known congenital anomaly, cervical incompetence, maternal medical disorder, and history of previous threatened preterm labor in current pregnancy. This study was conducted in November 2014 until Juni 2015.

Samples were obtained in the Outpatient Department of Obstetrics and Gynecology and Emergency Department in Sanglah General Hospital Denpasar, Bali. The serum ferritin evaluation was using ELISA in the Immunology Laboratory, while the IL-6 examination was using the Interleukin-6 Kit in the Pathology Anatomy Laboratory. The cut-off point for serum ferritin value to be considered high was if elevated more than 22.5ng/ml, while the IL-6 value was if elevated more than 6.14ng/ml.

Data was collected and analyzed using SPSS for Windows version 17.0. Descriptive analysis of the demographic data was involving maternal age, gestational age, and parity. Normality of data was evaluated with Shapiro-Wilk, the homogeneity of data was using Levene's and the comparative was using T-independent test with correlation test was using Chi-square test.

RESULTS

There were 20 samples of preterm labor cases with 20 samples of normal preterm pregnancy without sign of labor, with demographic characteristics were presented in the Table 1 below :

Table 1. Demographic Characteristics of the Subjects

Characteristics	Preterm Labor (Case) (n=20)		Preterm Pregnancy (Control) (n=20)		P-value
	Mean	**SD**	**Mean**	**SD**	
Maternal age (yrs)	24.15	5.82	23.60	3.75	0.724
Gestational age (wks)	32.05	1.40	31.05	1.91	0.066
Parity	1.95	0.95	1.95	0.76	1.000

Table2. Correlation between Serum Ferritin Level and Preterm Labor

		Group		OR	95% CI	P-value
		Case	**Control**			
Ferritin	High	16	9	4.89	1.20-19.94	0.022
	Low	4	11			

Table3. Correlation between Serum IL-6 value and Preterm Labor

		Group		OR	95% CI	*P-value*
		Case	Control			
IL-6	High	16	6	9.33	2.18-39.96	0.001
	Low	4	14			

There was no significant difference for all characteristics between two groups, with p > 0.05 for each variable. Table 2 shows there was correlation between serum ferritin level with preterm labor, with 5 fold increased risk of developing preterm labor (OR = 4.89, 95% CI = 1.20-19.94; p=0.022) compared to samples with low serum ferritin level. Table 3 also show similar result for correlation between serum IL-6 level with preterm labor, with 9 fold increased risk of developing preterm labor (OR = 9.33, 95% CI = 2.18-39.96; p=0.001).

DISCUSSION

Serum ferritin level is hypothesized to be as one of the risk factors in preterm labor through the preceeding mechanism of inflammation or infection. The initial proinflammatory cytokines is IL-1, which its increasing value will also increase the translation rate of serum ferritin that is mediated by IL-1β, which also promote the number of free ferrous released from ferritin or mitochondria. This was the basis of hypothesis why ferritin also can act as inflammatory biomarker or acute phase reactant.[7]

Moreover, IL-1 also increase IL-6 level if the inflammation or infection occurs.[6,8] Interleukin-6 is the cytokines that envolve in the process of inflammation and infection, regulating the metabolic process, and also regeneration.[9]Local response in the inflammation area will initiate the systemic inflammatory response that is induced by neuroendocrine changes such as pain, and also the release of systemic mediator such as arginine, vasopressine, corticotropine, and insulin-like growth factor.[9]

The other research was reporting that IL-1 and TNF were high in the amniotic fluid of pregnant women with preterm premature rupture of membrane. This cytokines were produced by decidua that was exposed with endotoxin, and both of them will trigger the decidua and amnion to produce prostaglandin that finally will initiates

preterm labor. The increasing level of IL-6 will also initiates the production of Metalloproteinase-9 (MMP-9), that will weaken the chorioamniotic layer which is prone to be ruptured due to degradation of collagen.[5]

Due to the role of IL-6 as the early biomarker in the inflammation cascade, the level of IL-6 is found to be increased after 3-4 hours exposure of endotoxin. As the result, in some research, the evaluation of IL-6 also used as the early detection for bacterial infection in neonates.[10]

CONCLUSION

The elevated level of serum ferritin and IL-6 were found to be the risk factor for preterm labor. As a consequechle, the evaluation of serum ferritin and IL-6 can be used for the early prediction of preterm labor. Thus the rate of preterm labor can be decreased, and the neonatal mortality rate can also be reduced.

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