High Maternal Cortisol Serum Levels as A Risk Factor for Preterm Labor

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ABSTRACT

Preterm delivery is the leading cause of death for children under 5 years of age worldwide. Preterm delivery is one of the significant factors causing neonatal death due to complications associated with preterm birth. Complications of preterm delivery account for about 16% of all deaths in children under 5 years, and 35% of total deaths of newborns. There are several broad outlines of factors associated with preterm labor, including stress, inflammation or infection, overdistention of the uterus and the hypothalamic-pituitary-adrenal axis. Several studies show the role of cortisol caused by these factors. This study aimed to assess the relationship of maternal serum cortisol levels with the risk of preterm delivery. This study used a case-control design conducted at Sanglah Hospital, Denpasar from May to August 2021. A sample of 50 women was obtained which was divided into case groups and control groups. Serum cortisol examination was performed on a 3 mL blood sample which was then examined using the ELISA method at the Integrated Biomedical Laboratory, Faculty of Medicine, Udayana University. The results were analyzed using the chi square test. There was no significant difference in the characteristics of the two groups. There was a significant relationship between high serum cortisol levels and the incidence of preterm labor in pregnant women (p < 0.001; 95% CI: 2.768-38.22; OR 10.29). High cortisol serum levels can increase the risk of preterm labor 10 times in pregnant women when compared to pregnant women with low cortisol blood serum levels.

Keywords: ELISA, cortisol, preterm delivery.

I. INTRODUCTION

Preterm delivery is the leading cause of death for children under five years worldwide. Preterm delivery is one of the significant factors causing neonatal death due to complications associated with preterm birth. Preterm delivery is also a major contributor to the loss of human potential due to neonatal morbidity. The prematurity that occurs due to preterm delivery is a major challenge in achieving the Millennium Development Goals (MDG)-4 goals because the possibility of neonatal mortality increases with the presence of prematurity.

The World Health Organization (WHO) defines preterm delivery as birth before 37 weeks of gestation, or less than 259 days from the first day of the last menstrual period. It is estimated that as many as 15 million babies are born preterm each year. About 1 million children die each year due to complications from preterm delivery. Complications of preterm delivery account for about 16% of all deaths of children under five years old and 35% of total newborn deaths [1]. According to data from WHO, Indonesia is ranked 5th as the country with the highest number of preterm deliveries globally [1]. Many children who survive lifelong experience disabilities, such as weak neurodevelopmental capacity, learning disorders, visual and hearing impairments, and secondary effects on long-term health that have substantial
consequences for families, social and health systems [2]. To date, the pathogenesis of preterm delivery is still not fully understood.

There are several broad outlines of factors associated with preterm labor, including stress, inflammation or infection, excessive uterine enlargement, and the hypothalamic-pituitary-adrenal (HPA) axis [3]. Cortisol is a very important hormone in the developing fetus and organ maturation, which are products end from the axis hypothalamic-pituitary-adrenal (HPA) and responsive to stress. The HPA axis controls the secretion of cortisol. The paraventricular nucleus produces Corticotropin-Releasing Hormone (CRH) in the hypothalamus. Stimulate the anterior pituitary to secrete Adrenocorticotropic hormone (ACTH), which acts on the adrenal cortex to secrete the hormone cortisol. Cortisol levels insufficient amount will hinder ACTH and CRH secretion as bait comes back negative. HPA Axis follows a rhythm circadian, where cortisol levels are high in the morning day and low at night day [4]. Maternal serum cortisol levels vary in pregnancy, reaching peaks in the second trimester and decreasing significantly in the third trimester [5]. Overview against 15 studies on cortisol and birth premature conclusion that the majority study with samples before age 23 weeks pregnant find a connection Between cortisol and birth premature, temporary analysis sample collected at age pregnancy next found still no consistent [1], [6].

Several studies have found that an increase in cortisol levels in pregnant women is a physiological condition, but cortisol levels have an abnormal increase [7]. Other studies have shown that stressful conditions, inflammation or infection, and psychological stress (anxiety or depression) that trigger preterm labor, are associated with high serum cortisol levels [8]. As previously described, the physiological stress response experienced by pregnant women involves changes in the HPA axis and the immune system. Under normal conditions, the HPA axis suppresses the inflammatory response, where there is a negative relationship between the HPA axis and inflammation. When proinflammatory cytokines are released into the bloodstream under physiological or inflammatory stress conditions, they trigger an increase in cortisol secretion. Cortisol produced will induce expression from PGHS but leading to down-regulation of PGDH. As a result, prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) are formed, which stimulate myometrial contractions and the onset of labor [7], [8].

A meta-analysis that assessed the association of cortisol levels with preterm delivery found that the ratio of plasma cortisol to corticosteroid-binding capacity (CBC) in a group of women who gave birth between 24 and 36 weeks of gestation was significantly higher than in a control group. With term delivery. Most studies suggest that maternal cortisol levels are positively associated with preterm delivery. Compared to women with term delivery, women who gave birth preterm had higher cortisol levels. However, in some studies, gestational age appears to influence the significance of the association between preterm delivery and maternal cortisol levels. Pregnant women with threatened preterm labor who have cortisol levels at the 55th percentile or above have a higher risk of delivery within 48 hours [8]. This study aimed to assess maternal serum cortisol levels with the risk of preterm delivery. This use design case-control study was conducted at Sanglah Hospital, Denpasar, from May to August 2021.

II. MATERIAL AND METHODS

Obtained sample as many as 50 women divided Becomes group cases and groups control. Serum cortisol test uses sample blood as much as 3 mL then checks the ELISA method in the Laboratory biomedical Integrated Udayana University. Results were analyzed using the chi-square test.

III. RESULTS

The characteristics of the study cover the age mother, age of the pregnancy, and index mass body (BMI). The characteristics subject can be seen in Table I. With the Kolmogorov-Smirnov normality test, the variables age mother, age pregnancy index mass body, and parity on both groups no obtained difference mean (p > 0.05).

Factor risk preterm delivery in a study is high serum cortisol levels in the blood. Analysis factor risk preterm delivery can be seen in Table II.

| TABLE I: CHARACTERISTICS AGE MOTHER, GESTATIONAL AGE, BMI, AND PARITY |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Variable | Case | Control | p |
| Age | 27.28±3.97 | 29.00±4.08 | 0.138 |
| Gestational age | 29.28±2.67 | 30.48±2.29 | 0.095 |
| BMI | 21.64±1.65 | 21.02±1.58 | 0.182 |
| Parity | 2.56±1.04 | 2.33±1.12 | 0.087 |

| TABLE II: NORMALITY TEST AGE MOTHER, AGE GESTATIONAL, BMI, AND PARITY |
|--------------------------|--------------------------|--------------------------|--------------------------|
| Variable | K-S statistics | df | Sig. |
| Age | 0.125 | 50 | 0.050 |
| Gestational age | -121 | 50 | 0.064 |
| BMI | 0.119 | 50 | 0.077 |
| Parity | 0.116 | 50 | 0.081 |

Study this look for factor risk high serum cortisol levels in blood with incident preterm delivery performed in the obstetrics and gynaecology at Sanglah Hospital Denpasar in May 2021 until total sample fulfilled. The researcher gets 50 incoming samples for criteria inclusion and criteria exclusion research. The average age of mothers in group preterm delivery is 27.28 years, with a standard deviation of 3.97. The average group preterm pregnancy was 29.00 with a standard deviation of 4.08, with a p-value = 0.138.

Factor age as factor risk with incident preterm labor still keeps researched because there is still a report of mutual research leave. A study previously explained the risk of increased preterm delivery moment age pregnant more from 35 years and will keep increasing with age pregnant more than 40 years and 45 years [9], [10]. Otherwise, other studies report that age elder mother not own connection with incident something threats preterm delivery in pregnancy. Study the
explain there are possible factors that are not observed that can influence preterm delivery, such as different characteristics health every individual, risk results birth bad before, and role factor genetics [11].

Results data research on samples found that the average pregnancy age in the group preterm labor group is 29.28 weeks with a standard deviation of 2.67. The mean pregnancy age in the group preterm pregnancy was 30.48 with a standard deviation of 2.29 p-value = 0.095. Cortisol concentrations in the fetus are ten times lower than the cortisol concentration in the mother.

However, maternal plasma cortisol is increased through stimulation of the HPA axis by placental corticotrophin-releasing hormone CRH, thereby causing increased fetal cortisol exposure, especially in pregnancies with attenuated 11βHSD2 expression [3], [8]. Many factors can attenuate the activity of the 11βHSD2 and should protect the fetus from exposed serum cortisol levels. Factors that can weaken 11βHSD2 are stress during pregnancy, nutritional factors, exposure to poor environments, and elevated cortisol [3]. State stress and depression During pregnancy could influence axis HPA activity in the body. When a stimulus occurs in the HPA axis, the hypothalamus secretes CRH, then the pituitary gland secretes adrenocorticotropic hormone, which stimulates the secretion of cortisol from the adrenal cortex. This situation causes serum cortisol levels to increase and can trigger something preterm delivery [8], [12].

In research, the mean BMI in group preterm delivery was 21.64 with a standard deviation of 1.65. The mean group preterm pregnancy was 21.02 with a standard deviation of 1.58 and a p-value = 0.182. Body mass index is one factor in the risk that affects incident preterm delivery in women pregnant with low BMI linked with state lack nutrition chronic with a deficiency in some element nutrition in the body including lack substance iron. Lack of nutrition in the body of pregnant women direct could influence the growth and development fetus inside the womb until it triggers something risk preterm delivery. Women pregnant with higher BMI also increase the risk of preterm delivery. The bigger the BMI value, the higher risk will happen in preterm delivery [10].

Research conducted by [3] supports the results study. Cortisol serum level could Become something sign or predictor for future preterm delivery. A study with a sample of 991 pregnant mothers reports serum cortisol high levels found in patients with spontaneous preterm delivery or premature preterm membrane rupture (PPROM).

Cortisol levels can be measured in plasma, serum blood, hair, saliva, and urine. Cortisol circulates in the blood in both free and bound forms. In plasma, cortisol is predominantly bound to corticosteroid-binding globulin (CBG), with a small amount loosely bound to albumin and the remainder free. In pregnancy, there are fluctuations in CBG that affect free cortisol, leading to changes in the relationship between total and free cortisol levels. Cortisol and total CBG levels increase during pregnancy, but the ratio of available CBG to cortisol decreases during pregnancy. The result is mild hypercortisolism in late pregnancy. Women pregnant with high cortisol levels in the blood could cause a threat to preterm delivery [8], [7].

### IV. CONCLUSION

Pregnant women with high serum cortisol levels own ten times at risk higher experiencing preterm delivery than pregnant mothers with a rate of cortisol not high.

### REFERENCES


