

# Correlation between Group B Streptococcus Infection in The Vagina with Maternal Serum C-Reactive Protein Levels in Preterm Labor

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## ABSTRACT

For decades GBS has been the most common cause of early-onset of neonatal infection. Ascending route infection with Group B Streptococcus bacteria increases the risk of preterm premature rupture of membranes, fetus infection, sepsis, preterm birth, and meningitis in infants. C-Reactive Protein is a sensitive marker of systemic inflammation where an increase in CRP can also be triggered by GBS infection. Objective of this study is to determine the relationship between Group B Streptococcus infection in the vagina of pregnant women and maternal serum C-Reactive Protein levels in preterm labor. The design of this study was cross-sectional in the preterm delivery population. This study was conducted in the obstetrics delivery room at Sanglah Hospital from January 2021 to January 2022. A total of 31 samples met the inclusion criteria, each of which was examined for vaginal swab culture and maternal serum CRP levels. Vaginal swab samples were processed at the Microbiology Laboratory of Sanglah Hospital, Denpasar. Maternal serum CRP samples were processed at the Clinical Pathology Laboratory of Sanglah Hospital, Denpasar. Bivariate analysis using Chi-square test. The relationship between GBS infection and maternal serum CRP levels using the Prevalence Ratio. The growth of Streptococcus agalactiae from vaginal swab culture was 7 samples (22.58%). Positive GBS in the group of high maternal serum CRP levels were found in 6 patients (19.4%) and the group of low maternal serum CRP levels as many as 1 patient (3.2%) while negative GBS in the group of high maternal serum CRP levels were found in 5 patients (16.1%) and 19 patients (61.3%) in the group of low maternal serum CRP levels. The Prevalence Ratio value obtained was 4.1 (1.78-9.49, 95% CI;  $p = 0.002$ ). There is a positive relationship between GBS infection and maternal CRP serum levels in preterm labor where positive GBS is a risk factor that increases maternal CRP serum levels in preterm labor.

**Keywords:** C-Reactive Protein, Group B Streptococcus infection, Preterm delivery.

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## I. INTRODUCTION

Preterm delivery is one of the main causes of newborn mortality. The prevalence of preterm delivery worldwide varies from 5% to 18%. According to WHO, preterm birth incidence is 15.5 per 100 live births in Indonesia, ranking it as the 9th highest in the world [1]. The incidence rate of preterm delivery varies between several government hospitals in Indonesia from 1.3% to 38.5% [2]-[8].

Preterm delivery is defined as delivery that occurs between 20 weeks of gestation and less than 37 weeks of gestation since last menstrual period [9]. Preterm delivery contributes to 75% of neonatal deaths and 50% of long-term morbidity. According to WHO [1], nearly one million children die each

year due to complication of preterm birth, which causes compensatory disturbances of neonate's respiratory, cardiovascular, gastrointestinal, central nervous, visual, skin, hematology, and immune system [10].

The same mechanism underlies both term and preterm delivery: an increase in uterine contractility, cervical ripening, and rupture of membranes to allow for delivery. Preterm delivery occurs due to a disease or pathological activation of one or more components of labor process, including anatomical, biochemical, immune, endocrine, and clinical change [11]. There are four pathways underlying causes of preterm delivery, namely: infection and inflammation, activation of maternal-fetal hypothalamus-pituitary-adrenal axis, decidual bleeding, and uterine stretch.

Each of the four pathway has its own distinct biochemical and biophysical pathway, but they all lead to same biochemical endpoint, which are uterotonics (prostaglandin, endothelial growth factors, platelet activating factors), activation and stimulation of myometrial, and degradation of extracellular matrix by metalloproteinase assisted by inflammatory cytokines and apoptosis resulting in Preterm Premature Rupture of Membrane (PPROM) and cervical maturation [12]. Prostaglandin is a crucial mediator determining the onset of labor because it induces myometrial contractions and stimulate proteolysis of cervical's extracellular matrix and membrane, causing cervical maturation and rupture of the membrane. PGE<sub>2</sub>, PGF<sub>2</sub> $\alpha$ , and activation of nuclear  $\kappa$ B factor also decrease functional progesterone by increasing expression ratio of progesterone isoform (PR-A and PR-B) receptors [11].

Infection is the most common cause of preterm delivery. Bacterial and viral infections spread through descending peritoneal tubal route, transplacental route, and ascending cervical route [13]-[15]. Ascending route is the most common route of infection, where microorganisms can enter through the cervical canal or upper vagina. Ascending infection is usually caused by normal vaginal flora or microorganisms, such as Group B Streptococcus (GBS), Mycoplasma vaginalis, and fungi [16]. Ascending infection has four stages. The first stage is the overgrowth of facultative and pathogenic organisms in the vagina and cervix. The presence of bacterial vaginosis is an early sign of first stage infection's spread. Chorionitis is in the second stage, when the bacteria have reached the decidua. The third stage of infection spreads into the bloodstream or into the amniotic cavity, resulting in amnionitis. The fourth stage occurs when aspiration of infected amniotic fluid causes congenital pneumonia or direct contact to the fetus [16], [17].

Group B Streptococcus (GBS) is a gram-positive coccus bacteria, normally found in the intestines, vagina, and rectum of pregnant women. Around 30% of pregnant women do not show clinical symptoms even though the birth canal contains GBS [18]. A correlation between GBS colonization and the prevalence of abortion, preterm delivery, and low birth weight (LBW) infants has been established by numerous studies. Premature births and LBW are closely linked to a severe GBS colonization in the cervicovaginal at 23 weeks to 26 weeks of gestation [19]. A meta-analysis of 45 studies on GBS colonies with preterm delivery found that in both cohort and cross-sectional studies, relative risk (RR) of preterm delivery on a pregnant woman with GBS colonies was 1.21 (95% CI,  $p = 0.061$ ). Whereas in the case control study, the odds ratio (OR) was 1.85 (95% CI,  $p = 0.003$ ) [20].

C-reactive protein is a sensitive marker of systemic inflammation synthesized in hepatocytes in response to infection and tissue damage [21]. Production of CRP is induced by the release of proinflammatory cytokines including Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Tumor Necrosis Factor Alpha (TNF- $\alpha$ ) which are released by bacterial infection products, such as lipopolysaccharides that activate macrophages. CRP is present in both acute and chronic inflammatory processes, while being frequently linked to acute inflammation. Prostaglandin is stimulated by the increase of inflammatory cytokines, which leads to uterine contractions and cervical ripening. Preterm delivery

is the result of the process. Reference shows an increased correlation of increased CRP in women with preterm delivery compared to healthy pregnant women [22]. Furthermore, it was found that women with CRP levels 7.5 mg/L had twice the risk of having preterm delivery compared to women with CRP levels  $< 2.0$  mg/L [23].

## II. MATERIAL AND METHODS

This research is a cross sectional study of the preterm delivery population, comparing population at risk (positive GBS culture) with population without risk (negative GBS culture). This study was conducted in the delivery room at Sanglah Hospital from January 2021 to January 2022 or until the required number of samples was obtained. Serum CRP levels were then examined for each group.

Inclusion criteria for this study are preterm pregnancy (gestational age between 20 weeks and 36 weeks 6 days), uterine contractions  $\geq 2x$  in 10 minutes, cervical ripening  $\geq 50\%$ , cervical dilation  $\geq 2$  cm, single live fetus, intact or ruptured amniotic fluid, and willing to participate in this study [24]. Exclusion criteria are placenta abruption, placenta previa, polyhydramnios, hypertension, diabetes mellitus, uterine fibroid, extra-genital infection, and receiving antibiotics within last 7 days.

Sample size is calculated using the Lemeshow formula. Samples are taken by consecutive sampling of preterm pregnant women in delivery room at Sanglah Hospital, who met the inclusion criteria. Sample selection was carried out through history, general, and obstetric physical examination of pregnant women who had preterm delivery in delivery room of Sanglah Hospital, Denpasar. Patients who agreed to participate in this study and met the inclusion criteria were required to fill the informed consent. Patients taking part in the study will have a vaginal swab and venous blood taken in the delivery room of Sanglah Hospital, Denpasar. Vaginal swab samples were then analyzed and processed at the Microbiology Laboratory of Sanglah Hospital, Denpasar for culture and examination for the presence of group B streptococcal bacteria. Venous blood taken was processed at the Clinical Pathology Laboratory, Sanglah Hospital, Denpasar to determine the levels of maternal serum CRP levels.

All data obtained were analyzed using Statistical Product and Service Solution (SPSS) version 16.0 application for Windows. Descriptive statistics include maternal age, gestational age, and parity. Chi-square test to determine the difference between positive and negative GBS test with high and low CRP levels in preterm delivery. Level of significance in this study is  $\alpha = 95\%$ . Prevalence ratio is calculated using a 2x2 table. If  $PR > 1$  then positive GBS is a risk factor for high CRP and  $PR < 1$  means positive GBS is a protective factor for high CRP.  $PR = 1$  means no association between GBS and CRP.

## III. RESULTS

This study involved 31 pregnant women with preterm delivery at Sanglah Hospital, Denpasar from June 2021 to August 2021. None of the patients who took part in this study

had COVID-19, despite the fact that the study was conducted during the COVID-19 pandemic.

According to Table I, the average maternal age was 28.19 ± 7.36 years old and average gestational age was 32 weeks 7 days ± 3 weeks 2 days. The mean parity was 0.77 ± 0.99. The average of maternal serum CRP level was 10.02 ± 13.10 with 11 samples (35.5%) had high CRP level and 20 samples (64.5%) had low CRP level. GBS was found positive on 7 samples (22.58%) and negative on 24 samples (77.42%).

Table II shows the findings of vaginal swab cultures performed on 31 patients. 4 samples (12.91%) had no bacterial growth, while of the 27 samples with positive culture result, 4 samples (12.91%) were RNF, 13 samples (41.94%) were CoNS, 7 samples (22.58%) were *Streptococcus agalactiae*, 1 sample (3.22%) was *Escherichia coli*, 1 sample (3.22%) was *Enterococcus faecalis*, and 1 sample (3.22%) was *Bacillus*.

TABLE I: CHARACTERISTICS OF PREGNANT WOMEN WITH PRETERM DELIVERY IN SANGLAH HOSPITAL, DENPASAR	
Variables	Sample (n=31)
Maternal age (mean ± SD)	28.19 ± 7.36
Gestational age (mean ± SD)	32 weeks 7 days ± 3 weeks 2 days
Parity (mean ± SD)	0.77 ± 0.99
0 (n, %)	16 (51.6%)
1 (n, %)	9 (29%)
2 (n, %)	3 (9.7%)
3 (n, %)	3 (9.7%)
Maternal Serum CRP level (mean ± SD)	10.02 ± 13.10
High (n ± SD)	11 (35.5%)
Low (n ± SD)	20 (64.5%)
Group B Streptococcus	
Positive (n, %)	7 (22.58%)
Negative (n, %)	24 (77.42%)

TABLE II: VAGINAL SWAB CULTURE RESULTS		
Variables	Sample (n)	%
Negative culture result	4	12.91%
Positive culture result		
RNF (Regional normal flora)	4	12.91%
CoNS (Coagulase-Negative Staphylococci)	13	41.94%
<i>Streptococcus agalactiae</i>	7	22.58%
<i>Escherichia coli</i>	1	3.22%
<i>Enterococcus faecalis</i>	1	3.22%
<i>Bacillus</i>	1	3.22%
Total	31	100%

TABLE III: ASSOCIATION BETWEEN GROUP B STREPTOCOCCAL INFECTION IN VAGINA AND MATERNAL CRP SERUM LEVELS ON PRETERM DELIVERY						
Variables	Maternal Serum CRP Levels		Total	PR	CI 95%	p
	High	Low				
Positive GBS (n, %)	6 (19.4%)	1 (3.2%)	7 (22.6%)	4.1	1.78 - 9.49	0.002
Negative GBS (n, %)	5 (16.1%)	19 (61.3%)	24 (77.4%)			
Total	11 (35.5%)	20 (64.5%)	31 (100%)			

Based on Table III, 6 samples (19.4%) had positive GBS result on high maternal serum CRP level (≥ 10 mg/dL) group, and 1 sample (3.2%) had positive GBS result on low maternal serum CRP level (< 10 mg/dL) group. Meanwhile, 5 samples

(16.1%) had negative GBS result on high maternal serum CRP level group and 19 samples (61.3%) had negative GBS result on low maternal serum CRP level group. The prevalence ratio (PR) value was 4.1 (1,78-9,49, CI 95%; p = 0,002). PR > 1 indicates association between GBS and maternal serum CRP level where positive GBS is a risk factor for high CRP on preterm delivery. The p value < 0.05 indicates that this study is significant.

#### IV. DISCUSSION

Preterm delivery remains a major public health concern in the fields of Obstetrics and Perinatology. Infection is one of the causes of preterm delivery. This observational study involved 31 pregnant women with gestational age ranging from 20 weeks to 36 weeks 6 days. The study's findings showed the mother was 28.19 ± 7.36 years old on average. Reference [25] shows different result, they found that women aged > 36 years old were associated with persistent colonization and higher rate of colonization on women aged > 40 years old. The average gestational age in this study was 32 weeks 7 days ± 3 weeks 2 days. Similar findings were found that preterm delivery often occurs at 28 weeks to 32 weeks of gestation [26]. Another study among patients who underwent preterm delivery had 28.5 weeks to 33 weeks of gestation [27]. In this study, the average parity was 0.77 ± 0.99 times. An increased risk of spontaneous preterm delivery at < 37 weeks of gestation in nulliparous women compared to their second pregnancy, with an OR of 1.95. Nulliparous women have the highest risk for preterm delivery [28].

Vaginal swab culture results were obtained from 31 samples, 7 (22.58%) of which were *Streptococcus agalactiae*. GBS was identified as one of the bacteria associated with preterm delivery [13]. Another descriptive methodological study found that prevalence of GBS colonization in pregnant women detected by culture method using Blood Agar (BA) and Chrome Agar (CA) without Todd Hewith broth was 9.4% whereas the prevalence by culture method using BA and CA enriched by Todd Hewith broth was 31.3% [29].

According to Table III, there is a significant association between GBS and maternal serum CRP levels (p = 0,002). PR value > 1 (PR = 4.1) indicates that positive GBS is a risk factor that increases maternal serum CRP levels, which leads to preterm delivery. A case-control study in China was conducted in 2021 with a sample of 371 pregnant women with gestational age more than 36 weeks. They found 59 samples (15.9%) with positive GBS infection and 512 samples (84.1%) with negative GBS infection. There was no significant difference in serum CRP level between GBS positive group and GBS negative group (3.5 mg/L and 3.2 mg/L, p = 0,530). Pregnant women with GBS infection had a higher risk of chorioamnionitis (p = 0,001). They also found that pregnant women with chorioamnionitis had higher serum CRP levels compared to healthy pregnant women (12.3 mg/L and 3.2 mg/L, p = 0,002). CRP significantly correlates with an increased risk of chorioamnionitis (OR 1.063; 95% CI: 1.028-1.098); p < 0,001) [30].

GBS is an opportunistic pathogen bacterial that is commonly tested before delivery. GBS colonizes in the gastrointestinal tract and birth canal. Invasive GBS infection is an important cause of neonatal disability and death [31].



Preterm delivery, neonatal encephalopathy, and stillbirth are significantly associated with GBS infection [10], [32], [33]. GBS colonies cause prematurity and low birth weight when they occur between 23 weeks to 26 weeks of gestation. A reduction in the spread of germs to newborns during labor can be seen in women receiving intrapartum treatment who have positive cultures for GBS [34]-[36].

Infection releases bacterial products such as lipopolysaccharides which activate macrophages and other cells to produce and release various cytokines such as Tumor Necrosis Factor Alpha (TNF- $\alpha$ ), Interleukin-1 (IL-1), and Interleukin-6 (IL-6). These cytokines are proinflammatory cytokines, which stimulates the liver to synthesize and release a number of plasma proteins such as acute phase proteins, including C-Reactive Protein (CRP) which can increase 1000 times, making CRP one of the markers for evaluating inflammation or tissue damage (necrosis) [37].

## V. CONCLUSION

Based on this research, it can be concluded that GBS infection in pregnant women can cause preterm delivery and an increase in maternal CRP serum levels.

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