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Chorioamnionitis and Funisitis Increase the Risk of Preterm Labor and Early Onset Neonatal Sepsis

KT SURYA NEGARA[1], SM RYAN[1], W ENDANG[2], EVERT PANGKAHILA[1], AP WIRADNYANA[1] and STELLA KAWILARANG[2]

[1]Maternal-Fetal Division, Departement of Obstetrics and Gynaecology, Udayana University Sanglah Hospital Bali.
[2]Resident of Departement Obstetrics and Gynecology, Udayana University Sanglah Hospital Bali.
*Corresponding author E-mail: tutsuryanegara@gmail.com

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ABSTRACT

Preterm labor is one of the main problem in obstetrics, especially in the perinatology aspect related to the morbidity and mortality of neonates. The inflammation of placenta and amniotic membrane becomes as the risk factor for preterm labor, premature rupture of membrane and infection of neonates. This study was designed to investigate the correlation of chorioamnionitis and funisitis as the risk factor of preterm labor and early onset neonatal sepsis. This study was designed using analytic observational prospective cohort study with internal control. Study was conducted in the Delivery Ward of Obstetric Emergency Room Sanglah General Hospital in May until November 2012. The mean result of neonates' body weight and length for the preterm group were significantly different compared to the aterm group ($p<0.05$). The body temperature and the hemoglobin level were not different significantly ($p>0.05$). The relative risk (RR) of the amniotic membrane inflammation towards preterm labor was 4 (RR=3.86, 95% CI=1.61-929, p=0.001) compared to the normal amniotic membrane, while the RR towards neonatal sepsis was 9 (RR=9.27, 95% CI=1.29-66.93, p=0.007). The RR of the umbilical cord inflammation towards preterm labor was 3 (RR=3.18, 95% CI=1.13-8.98, p=0.008), while the RR towards neonatal sepsis was 5 (RR=5.20, 95% CI=0.72-37.76, p=0.084). Incidence of inflammation within decidua, chorion or amnion increase the risk of preterm labor. This study shows that the pathological chorioamnionitis and funisitis increased the risk of preterm labor and early onset neonatal sepsis.

Keywords: Chorioamnionitis, Funisitis, Preterm birth, Early onset neonatal sepsis.

INTRODUCTION

Preterm labor is one of the main obstetrical problem, especially in perinatology issue, where preterm babies occur as the etiology of neonatal morbidity and mortality in developed and developing countries. There was an increase in the rate of preterm birth to 12.3% in 2003, with the rate of infant mortality increase to 7.0 per 1,000 live births in 2002[1].

The incidence of preterm labor is varied throughout the world. Data estimation was stating that preterm birth rates range from 25% in the developing countries, while it was only 5% in the developed countries[2]. In Indonesia itself, the incidence of preterm labor was about 10-20%[3], while in Sanglah General Hospital Denpasar was 7.44% in 1996[4]. Ardhana stated that the study in Sanglah General Hospital Denpasar in 1999 showed 431 preterm labor among 4,984 labor (8.65%) and also Udiarta stated similar results for the study in 2001 which was 6.82%, in 2002 was 7.50% and in 2003 was 11.4%[5].

The etiology of preterm labor is not fully understood. Few concepts explain the underlying mechanism of preterm labor, which is almost

always correlated with the infection inside amniotic fluic, ischemia of the uteroplacental circulation, overdistension of the uterus, endocrine disorder, or abnormal immune response in mother or fetus. Lockwood stated that the correlation between the incidence of preterm labor and the inflammation process occur in the decidual tissue, chorion and amnion[6].

Infection is the most common etiology of preterm labor and premature rupture of membrane, which bacteria spread toward uterus and amniotic fluid to trigger inflammation and cause preterm labor and premature rupture of membrane. The pathophysiology of premature rupture of membrane in the infection pathway is mentioned by Goldenberg (2000). Bacterial invasion in choriodecidual tissue will trigger the release of endotoxin, exotoxin, and activate decidual and fetal membrane to produce various cytokines such as TNF-á, IL-á, IL- 1â, IL-6, IL-8 and granulocyte colony-stimulating factor (GCSF). Cytokines, endotoxin and exotoxin will trigger the formation and release of prostaglandin, initiate neutrophil chemotaxis, infiltration and activation, and finally the formation and release of metalloproteinase and the other bioactive substances. Prostaglandin will trigger the uterus contraction, while metalloproteinase invasion in the chorioamnion membrane will cause preterm labor and rupture of amniotic membrane[7].

Current evidence shows that about a third of spontaneous preterm labor incidence is related with intrauterine infection through their products, such as bacterial toxin, bacteria phospholypase and cytokine[8]. The problem is that the manifestation of intrauterine infection is chronic and asymptomatic during pregnancy until the onset of labor, or the rupture of chorioamnion membrane is caused by the prostaglandin stimulation that trigger the onset of preterm labor. Study by Salafia et al in 1989 showed that chorioamnionitis occured in 4% of aterm labor without complication, and 1.2% among them was asymptomatic chorioamnionitis[9]. The accepted standard criteria to diagnose chorioamnion infection is with the culture of the chorioamnion membrane or histology examination. However, it cannot be routinely performed to evaluate any intrauterine infection for those patients who are not in labor. Candra et al study in 1998 showed that the incidence of preterm labor occured in the histopatholoic-proven chorioamnionitis (69.7%) compared to the non-chorioamnionitis (22.6%)[10]. The prevalence of microbes infection in the amniotic fluid that was detected by the culture of amniotic fluid was 4.2%-21.6% among the preterm labor cases with intact chorioamnion membrane. The asymptomatic intraamnion infection could be fever, uterine tenderness, fouly odor of the amniotic fluid, fetal tachycardia, maternal tachycardia, and maternal leucocytosis which occur late. It was based on the study of Romero et al in 1989 that showed only 12.5% of all samples with intraamniotic infection. As the result, early detection of the intraamniotic infection is difficult[11].

Neonatal sepsis can be caused by the intraamnion infection or chorioamnionitis. Intraamnion infection occurs in 3.3% of aterm premature rupture of membrane, which complicates about 6-12% of all pregnancy. Chorioamnionitis commonly occurs in pregnancy that is related with poor maternal and perinatal outcome, and also poor long term complication. Study by Soraisham in 2009 showed that the poor maternal outcome included postnatal infection and sepsis, while neonatal outcome was stillbirth, prematurity, neonatal sepsis, chronic pulmonary disease, and brain damage that cause cerebral palsy and other neurodevelopment defect. Preterm babies also have higher complication of chorioamnionitis compared to the aterm babies, including perinatal death (25% vs 6%), neonatal sepsis (28% vs 6%), pneumonia (20% vs 3%), grade 3 or 4 intraventricular bleeding (24% vs 8%), and respiratory distress (62% vs 35%). In general, chorioamnionitis is correlated until 40% of the early onset neonatal sepsis incidence[12].

The management of preterm labor still need to be improved in order to prevent the incidence, by understanding the pathophysiology of preterm labor in depth. As the result, the prevention and management of preterm labor will be improved and the incidence of neonatal sepsis can be avoided.

METHODS

This study was using the analytic observational cohort prospective study with internal control, which was conducted for 7 months (May –

November 2012). The study sample was 28 pregnant women, who was admitted to Obstetric Emergency Ward with preterm labor that was suspected caused by the inflammation of amniotic membrane and placenta, fulfilled the inclusion and exclusion criteria, and willing to join with the study after signed the informed consent. Data was analyzed with Chi-square test, with all variables were evaluated for the relative risk (RR) and attributable risk (AR). The logistic regression test was conducted to analyze the effect of independent and concomitant variable towards the outcome (dependent).

RESULT

In June – December 2012, there were 28 pregnant women who were admitted to Obstetric Emergency Ward with preterm labor, that was suspected to be correlated with amniotic membrane and placental inflammation. These samples were chosen after fulfilled the inclusion and exclusion criteria. Based on the characteristics of the sample study, the mean baby birth weight and length for the sample group was significantly different compared to the control group ($p<0.05$), while the temperature and hemoglobin level were not significantly different ($p>0.05$).

Based on the chi-square test, the relative risk of amniotic membrane inflammation towards preterm labor was 4 (RR=3.86, 95%CI = 1.61-9.29, p=0.001) compared to the normal amniotic membrane. While the relative risk of umbilical cord inflammation toward preterm labor was 3 (RR=3.18, 95%CI = 1.13-8.98, p=0.008) compared to the normal umbilical cord.

The relative risk of amniotic membrane inflammation toward neonatal sepsis was 9 (RR=9.27, 95% CI = 1.29-66.93, p=0.007) compared to the normal amniotic membrane. While the relative risk of umbilical cord inflammation toward neonatal sepsis was 5 (RR=5.20, CI 95% = 0.72-37.76, p=0.084) compared to the normal umbilical cord.

DISCUSSION

This study result was supported by Shobokshi study result in 2002, which stated that about a third of spontaneous preterm labor was correlated with the intrauterine infection through their products such as bacterial toxin, bacterial phospholipase and cytokines. Moreover, it was known that the manifestation of intrauterine infection was chronic and asymptomatic during pregnancy until the onset of labor or the rupture of chorioamnion membrane due to prostaglandin stimulation that causing the onset of preterm labor. The latest study showed that about 26% of spontaneous preterm labor with intact chorioamniotic membrane also having asymptomatic intraamniotic infection[11].

The prevalence of microbes infection in amniotic fluid that was detected from the culture of amniotic fluid was 4.2%-21.6% among all preterm labor patients with intact chorioamniotic membrane. The asymptomatic intraamnion infection such as fever, uterine tenderness, fouly odor of amniotic fluid, fetal tachycardia, maternal tachycardia and maternal leucocytosis which occur late, were similar with the result of another study[13]. It showed that only 12.5% of all patients were proven with intraamnion infection, and made the early detection of intraamnion infection is difficult[11]. Intraamniotic infection or chorioamnionitis can cause neonatal sepsis, where it occured about 3.3% in aterm premature rupture of membrane and cause about 6-12% of complication in pregnancy. Chorioamnionitis is commonly occur in pregnancy that correlates with poor maternal and neonatal outcome, and also poor long term complication.

Moreover, the study by Soraisham in 2009 showed that the poor maternal outcome were including the postnatal infection and sepsis, while the neonatal outcome were stillbirth, prematurity, neonatal sepsis, chronic pulmonary disease, and brain damage that causing cerebral palsy and other neurodevelopmental defect. Preterm babies were having higher complication from chorioamnionitis compared to the aterm babies, including perinatal death (25% vs 6%), neonatal sepsis (28% vs 6%), pneumonia (20% vs 3%), grade 3 or 4 intraventricular bleeding (24% vs 8%), and respiratory distress (62% vs 35%)[12].

In general, chorioamnionitis is correlated in almost 40% of the early onset neonatal sepsis. This fact shows that early management to prevent the preterm labor that was caused by asymptomatic

intraamniotic infection is needed, so there will be a quick yet specific and sensitive test to indentify any microorganism invasion towards amnion. The most appropriate sample to detect intraamnion infection is the amniotic fluid, with decrease of glucose level, increase level of leucocytes, C3 complement and various cytokines compared to the amniotic fluid from normal samples. The standard accepted criteria to diagnosis chorioamniotic infection is by performing culture of the chorioamnion or histology examination.

The etiology of preterm labor is usually can not be determined, which few concepts of the etiology usually correlated with infection of amniotic fluid, uteroplacental ischemia, overdistended uterus, endocrine disorder and abnormal immune response from the mother and the fetus. Lockwood study stated that there was correlation of the preterm labor incidence with the inflammation in the decidua, chorion and amnion[14].

Salafia et al study in 1989 showed that there were few chorioamnionitis severity in 4% of aterm pregnancy without complication, which 1.2% among them was asymptomatic chorioamnionitis[9]. While the study that was conducted by Candra et al in 1998 showed that the incidence of preterm labor in the histopathology-proven chorioamnionitis was 69.7% compared to the non chorioamnionitis (22.6%)[10].

Various pathogen such as bacteria, virus, parasite, or fungi can cause severe infection that can cause sepsis. The pattern of sepsis etiology also different among countries and period of time. Even in the developed countries itself, there were

Table 1 : Characteristics of Study Sample for the Preterm and Aterm Baby

Variables	Labor		p
	Preterm	Aterm	
Body weight	1887,14±384,42	2966,43±656,51	0,001
Body length	41,14±3,51	47,79±4,02	0,001
Temperature	36,38±0,37	33,94±9,77	0,360
Hemoglobin	16,30±2,24	17,36±3,91	0,428

Table 2: The Role of Choriomnionitis and Funisitis to Preterm Birth Development

		Labor		RR	95% CI	P-value
		Preterm	Aterm			
Amniotic membrane	Inflammation	10	1	3,86	1,61-9,29	0,001
	Normal	4	13			
Umbilical cord	Inflammation	11	4	3,18	1,13-8,98	0,008
	Normal	3	10			

Table 3: The Role of Chorioamnionitis and Funisitis to Sepsis Development

		Sepsis		RR	95% CI	P-value
		Sepsis	Normal			
Amniotic membrane	Inflammation	6	5	9,27	1,29-66,93	0,007
	Normal	1	16			
Umbilical cord	Inflammation	6	9	5,20	0,72-37,76	0,084
		1	12			

different pattern of pathogenesis, which neonatal sepsis is mostly caused by Gram negative bacteria. The pattern of pathogens that causing sepsis in the developing countries were studied by the World Health Organization Young Infants Study Group in 1999. The study was performed in four developing countries such as Ethiopia, Phillippines, Papua New Guinea, and Gambia.

Different pattern of pathogens that causing sepsis within developing countries was investigated by the World Health Organization Young Infants Study Group in 1999. The study was conducted in 4 developing countries such as Ethiopia, Phillipines, Papua New Guinea and Gambia. This study states that the most common pathogen found in the blood culture was Staphylococcus aureus (23%), Streptococcus pyogenes (20%), and E.Coli (18%). From the cerebrospinal fluid sample that was obtained from the early onset neonatal sepsis, the most common pathogen was the Gram Negative bacteria such as Klebsiella and E.Coli, while the most common pathogen from the late onset neonatal sepsis was Streptococcus pneumoniae serotype 2. E.coli was commonly found in the neonates who were delivered not in the hospital, and also found in the vaginal swab that was obtained from the rural area women. While Klebsiella was commonly isolated from the neonates who were delivered in the hospital. Other than those pathogens, the other commonly found species were Pseudomonas, Enterobacter and Staphylococcus aureus. In Cipto Mangunkusumo Hospital / Faculty of Medicine University Indonesia in 2002, the most common isolated pathogens were Enterobacter sp, Acinetobacter sp., Coli sp., Coagulase-negative staphylococci, Staphylococcus aureus, E. coli, Klebsiella, Pseudomonas, Candida, Streptokokus Grup B, Serratia, Acinetobacter, and anaerobes bacteria.

The pattern of sepsis etiology is different among different centres and period, and also the onset of the sepsis itself. Based on the NICHD Neonatal Network Survey in 1998-2000 towards 5447 low birth weight babies (BW<1500gr) with early onset neonatal sepsis (EONS) and 6215 low birth weight babies with late onset neonatal sepsis (LONS), it showed that there were about 1.5% of bacteremia in the EONS and 21.% in the LONS. There were Gram negative bacteria in 60.7% of bacteremia in the EONS, while the LONS bacteremia was most commonly caused by the Gram positive bacteria (70.2%). The most common Gram negative bacteria in the EONS was E.coli (44%), while for the LONS was Coagulase-negative Staphylococcus (47.9%).

Infection is not a static condition, where any pathogen in the bloodstream (bacteremia, viremia) can cause the sequelae of infection (FIRS : Fetal Inflammatory Response Syndrome or SIRS : Systemic Inflammatory Response Syndrome), and continue to sepsis, severe sepsis, septic shock, multi organ failure and finally death. According to the infant development stage, the physiologic and laboratory variables in the SIRS concept are different based on their age. The International Concensus Conference on Pediatric Sepsis in 2002 stated that there was an aggrement of the definition in SIRS, sepsis, severe sepsis, and septic shock. Based on that aggrement, the definition of neonatal sepsis is if there is SIRS condition that is triggered by the infection, whether it is only suspected or already proven.

CONCLUSION

Pathological chorioamnionitis and funisitis increase the risk of preterm labor and early onset neonatal sepsis . The severity of the chorioamnionitis are related to the higher risk of preterm labor.

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