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RESEARCH ARTICLE

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Association Of Gestational Age And Birth Weight With Neonatal Sepsis In Ulin Hospital Banjarmasin

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Abstract:

Indonesia is ranked 7th in the country with the highest neonatal mortality rate in the world, respectively 60.000 neonatal deaths per year. Neonatal sepsis in one of the major causes of neonatal death. The aim of this study is to find the association of gestational age and birth weight with the incidence of neonatal sepsis in Ulin Hospital Banjarmasin, January-December 2021. This study is a retrospective study with a cross sectional approach at Neonatal Ward, Ulin Hospital Banjarmasin, South Borneo, January to December 2021. The total sample was 200 infants consisting of 100 healthy infants and 100 sepsis infants. The source of gestational age, birth weight, and diagnosis data were taken through patient medical records. The mean gestational age of healthy infant group was 38,45 weeks (all infants were at term) while in septic infant group was 33,59 weeks (70%preterm, 28%at-term, and 2%post-term). The average birth weight of healthy infant group was 3021.24 grams (all infants were normal birth weight) while in septic infant group was 2003,59 grams (25%normal birth weight, 40%low birth weight, 25%very low birth weight, and 10%extremely low birth weight). There were an association of gestational age and birth weight with neonatal sepsis, confidential rate was 95%. ($p<0,000$ and $p<0,000$). There were an association of gestational age and birth weight with neonatal sepsis in Ulin Hospital Banjarmasin, January-December 2021.

Keywords: Birth weight; Gestational age; Neonatal sepsis

Introduction

Neonatal sepsis defined as a systemic inflammatory syndrome in response to a suspected infection, with or without bacteremia which accompanied by positive blood culture in the first 28 days of life.[1] In 2020, globally there are 17 neonatal deaths per 1.000 births and 6.500 neonatal deaths every day based on United Nations International Children's Emergency Fund (UNICEF). The Saharan African continent and South Asia are ranked 1st and 2nd highest in child mortality, especially neonates in the world.[2] Based on World Health Organization in 2019, Indonesia is ranked 7th in countries with the highest neonatal mortality, 60.000 neonatal deaths per year. Globally, the most common causes of neonatal death are premature birth, complications related to the birth process, infections, and congenital abnormalities.[3]

Based on Indonesian Health Profile in 2020, there were 28.158 under-five deaths and 72% of these deaths occurred in neonatal period (20.266 deaths). The most common causes of neonatal death in Indonesia (2020) were Low Birth Weight (LBW) (35,2%), asphyxia (27,4%) and others (22,5%).[4] The neonatal mortality rate in South Borneo in 2020 is 7,5 per 1.000 live births.[5] In 2021, neonatal sepsis is the most common cause of death which is 45,5% in High-Risk Neonatal Installation (INRiT) Ulin Hospital Banjarmasin. Neonatal sepsis risk factor are influenced by maternal and infant factors. Maternal factors such as maternal infection, premature rupture of membranes, low socioeconomic status, history of inadequate ante natal care, mode of delivery, number of parities, and maternal age. Neonatal factors include prematurity, low birth weight, low APGAR score, asphyxia, and history of postnatal resuscitation.[6,7]

A meta-analysis study by Belachew et al in 2020 mention that neonatal sepsis was strongly associated with gestational age and birth weight (OR= 3,36 and OR=1,42). Preterm infants have a higher risk 3,36 times to experience neonatal sepsis than at term infants. Low birth weight infants are 1,42 times more likely to experience neonatal sepsis than infants with normal birth weight.[8]

Case control study by Rachmawati in 2021 mention that there is an association between low-birth-weight infants with neonatal sepsis at Perinatology Ward, Dr. H. Abdul Moeloek Hospital in Lampung (p=0,004, OR 3,857).[9]

Case control study by Harum et al in 2021 mention that there is a significant relationship between premature infants (<37 weeks) with neonatal sepsis (p=0,001; OR=7,78). Very extreme preterm infants (<28 weeks) and extreme preterm infants (28-32 weeks) are strongly associated with higher mortality rate in neonatal sepsis (p=0,043 and p=0,032).[10]

The aim of this study was to analyze the association between gestational age and birth weight with the incidence of neonatal sepsis.

Research Method

This study is a retrospective study with a cross sectional approach that aims to assess the association between gestational age and birth weight with the incidence of neonatal sepsis. This study take place in High-Risk Neonatal Installation (INRiT) Ulin Hospital, Banjarmasin, South Borneo, from January-December 2021. The inclusion criteria in this study were all patients diagnosed with sepsis, both clinically or proven with positive culture. Data for gestational age, birth weight, and diagnosis of sepsis were obtained from patient medical records. This study was approved by the committee of ethics Ulin Hospital Banjarmasin.

The data in this study processed using software SPSS 26 for MacBook. The normality test proceeds with Kolmogorov-Smirnov Test, if the data is normally distributed then the

analysis will be continued with Unpaired T Test; and if the data is not normally distributed then the analysis will be continued with alternative – Mann Whitney Test. The data analysis in this study is processed with a confidence level of 95%.

Results

This study consists of 100 infants diagnosed with sepsis and 100 healthy infants as a control group. The basic characteristics of the subjects in this study can be seen in Table 1.

Table 2 includes data on gestational age of two group in this study. The mean gestational age in the control group was 38,45 weeks (all infants born at term), while the mean gestational age in the case group was 33,59 weeks (majority born with low birth weight). Infants in the case group consist of 70 (70%) infants preterm, 28 (28%) infants at term, and 2 (2%) infants post term. Data analysis using the Kolmogorov Smirnov Test showed that the data was not normally distributed ($p<0,05$). Data analysis was continued using the Mann Whitney Test with confident level of 95%. Analysis of gestational age data for the control group and case group using the Mann Whitney Test obtained a p-value of 0,000 and z value -8,984 ($p<0,05$), which means that there is an association between gestational age with the incidence of neonatal sepsis.

Table 3 includes data on birth weight of two group in this study. The mean birth weight in the control group was 3.021,24 grams, while the mean birth weight in the case group was 2.003,58 grams. In case group infants, there were 40 (40%) infants with low birth weight (<2.500 grams), 25 (25%) infants with very low birth weight (1.000-1.500 grams), and 10 (10%) infants with extremely low birth weight (<1.000 grams). Data analysis using the Kolmogorov Smirnov Test showed that the data was not normally distributed ($p<0,05$). Data analysis was continued using the Mann Whitney Test with confident level of 95%. Analysis of birth weight data in the control group dan case group using the Mann Whitney Test obtained p value 0,000 and z value -8,049 ($p<0,05$), which means there is an association between birth weight with the incidence of neonatal sepsis.

Table 1. Basic Characteristics.

Characteristic	Control Group (n=100)	Case Group (n=100)
Sex		
Male	49	56
Female	51	44
Delivery mode		
Spontaneous	61	36
Sectio Caesarea	39	58
Vacuum Extraction	0	6
Parity	2,24	2,46
Maternal age	29,7 years	31,6 years
Mayor Risk Factor	0	0,59
Minor Risk Factor	0,18	1,53
Length of stay	0,42 days	13,66 days
Discard Condition		
Healthy	100	74
Death	0	24
Against medical advice	0	2

Table 2. Gestational Age Data.

	Control Case (n=100)	Case Group (n=100)	P value
	Mean (SD)	Mean (SD)	
Gestational Age	38,45 (0,91)	33,59 (4,32)	0,000
Pre term	0	70%	
At term	100	28%	
Post term	0	2%	

Table 3. Birth Weight Data.

	Control Group (n=100)	Case Group (n=100)	P-value
	Mean (SD)	Mean (SD)	
Birth Weight	3021,24 (332,14)	2003,58 (858,82)	0,000
Normal Birth Weight	100	25%	
Low Birth Weight (LBW)	0	40%	
Very Low Birth Weight (VLBW)	0	25%	
Extremely Low Birth Weight (ELBW)	0	10%	

Discussion

This study is a retrospective study from patient medical records at the High-Risk Neonatal Installation (INRiT) at Ulin Hospital Banjarmasin, from January-December 2021. The total sample in this study were 200 infants consisting of 100 septis infants and 100 healthy infants. Neonatal sepsis defined as a systemic inflammatory syndrome in response to a suspected infection, with or without bacteremia, accompanied with positive culture in the first 28 days of life.[1]

Sample in this study consist of 100 sepsis infants (56% male and 44% female) and 100 healthy infants (49% male and 51% female). Agnche et al study in 2019 in Ethiopia mention that male infants were 3,7 times more likely to experience neonatal sepsis than female infants.[11] There were a difference in expression of pro and anti-inflammatory cytokines that were influenced by gender, for example, pro-inflammatory cytokines (IL-6 or procalcitonin) were found to be higher in male infants that in female infants with sepsis. Androgen hormones in male infants have the effect of suppressing cell-mediated immune responses; on the contrary, estrogen and its precursors in female infants have a protective effect so that it can be a natural advantage for female infants against the incidence of sepsis.[12]

Delivery mode characteristic in 100 infants of sepsis group in this study consist of 58 (58%) infants were born by caesarean section, 36 (36%) infants were born spontaneously per vagina, and 6 (6%) infants were born by vacuum extraction. Noah et al study in 2022 mention that infants born by caesarean were more at risk of developing neonatal sepsis than babies born

spontaneously per vagina. This is related to an increased risk of infection transmission from caesarean procedures and underlying disease that indicate caesarean procedure.[13] Research on Australian women in 2021 who underwent caesarean stated that there was a decrease in the systemic immune function of infants born by caesarean. There was a decrease in the expression of TLR-2 and TLR-4 in infants born by caesarean; which play an important role as mediators in the formation of natural immunity, this may cause infants born by caesarean are more vulnerable to bacteria and viruses.[14]

Maternal risk factors (especially premature rupture of membranes) and the possibility of fetal infection during pregnancy are strongly associated with the incidence of neonatal sepsis.[15] In this study, the mean mayor and minor risk factor in sepsis group is higher than in control group. Andrade et al study in 2019 mention that there was relationship between maternal risk factor with neonatal sepsis with p value 0,005.[16]

The mean length of stay in sepsis group in this study was 13,66 days, longer than in control group which was less than a day. Adatara et al study in 2018 in Ghana mention that infants who were hospitalized for approximately 14 days were 16,6 times more likely to develop sepsis compared to infants who were hospitalized less than 7 days. A longer length of stay can lead to an increased risk of nosocomial infections due to an immature immune system in infants.[17]

Association of Gestational Age with Neonatal Sepsis at Ulin Hospital Banjarmasin

The mean gestational age in the sepsis group in this study was 33,59 weeks compared to 38,45 weeks in the control groups. Infants in the sepsis group consist of 70 (70%) infants born pre term, 28 (28%) infants born at term, and 2 (2%) infants born post term. Data analysis using the Kolmogorov Smirnov Test showed that the data were not normally distributed ($p<0,05$), then the data analysis was continued with the Mann Whitney Test with confidence level of 95%. Analysis of gestational age data of case and control groups conclude that there was an association between gestational age with neonatal sepsis in Ulin Hospital, that preterm infants were associated with the incidence of neonatal sepsis ($p=0,000$, $z= -8,984$).

Belachew et al study in 2020 in Ethiopia mention that the incidence of neonatal sepsis was strongly associated with gestational age. Preterm infants have higher risk 3,36 times to develop neonatal sepsis than at term infants. Infants born pre term (<37 weeks) have a higher risk of infection that can lead to death.[8]

Addisu et al study in 2018 mention that the incidence of meconium-stained amnion increases with increasing gestational age. Infants born post term (>42 weeks) are at risk for meconium aspiration syndrome.[18]

Shrestha et al study in 2018 stated that meconium aspiration syndrome was one of the causes of neonatal sepsis that contributed to death related to neonatal sepsis ($p=0,008$).[19]

Premature infants may not have developed mature immune system, either innate or adaptive immunity. The immune system in preterm infants can be influenced by many factors related to prematurity itself. The number of monocytes and neutrophils in preterm infants was found lower than at term infants. The function of cells in killing pathogens was found to be lower than at term infants; in addition, lower T cell production would inhibit T cell activation and decrease the ability to kill bacteria or detect viruses inside cells.[14]

Gestational age greatly affects the maturity of the neonatal immune system. The immune system in neonates undergoes a controlled maturation process as show in **Figure 1**. The infant's immune system also

depends on transfer antibodies from the mother. The transfer of antibodies across placenta from mother to infants begins significantly at 20 weeks gestation, therefore preterm infants have lower IgG levels that at term infants. IgG transfer to infant in the first trimester is minimal, approximately 10% at 17-22 weeks' gestation, 50% at 28-32 weeks' gestation. Immunoglobulin G is a specific immune system that pre-dominates against gram negative and opsonic bacteria. Humoral protection in preterm infants is less efficient against pathogens than at term infants who receive trans-placental transfer from the mother which prevent them from infection. [20,21]

After birth, pre term infants begin to rapidly produce B-cell repertoires, the expression of IgG and IgA repertoires maintain fetal characteristics such as short CDR-H3, genetic diversity and bias, and low somatic mutations. This molecular characteristic causes preterm infants to produce fewer antibodies with lower antigen affinity for the vaccination response. The differentiation of secondary antibody repertoire in pre-term infants proceeds more slowly than at term infants so that preterm infants are more susceptible to infection than at term infants.[21]

Association of Birth Weight with Neonatal Sepsis at Ulin Hospital Banjarmasin

The mean birth weight in sepsis group was 2.003,58 grams (majority born low birth weight) while in control group was 3.021,24 grams (all infants born with normal birth weight). In the sepsis group, 25% of infants with adequate birth weight and 75% of LBW infants (<2.500 grams) consist of 40% of LBW infants, 25% of VLBW infants, and 10% of ELBW infants. Data analysis by Kolmogorov Smirnov Test obtained data that was not normally distributed (p<0,05), then data analysis was continues using the Mann Whitney Test with a confidence level of 95%. Analysis of birth weight in the sepsis dan control groups found that there was an association between birth weight with the incidence of neonatal sepsis in Ulin Hospital, that low birth weight infants was associated with the incidence of neonatal sepsis (p=0,000, z= -8,049).

A descriptive study by Amaliya in 2020 at Perinatology Room of the East Java Hospital, mention that the majority of infants with sepsis were born preterm and had low birth weight. This study concludes that there were 53% infants born pre term and 65% born with low birth weight had early onset sepsis.[22]

Adara et al study in 2018 in Ghana mention that infants with birth weight <1.500 grams are 2,54 times more likely to develop neonatal sepsis compared to infants with normal birth weight.[17] In addition, research by Belachew et al in 2020 in Ethiopia stated that infants with birth weight <2.500 grams are 1,42 times more likely to experience neonatal sepsis than infants with normal birth weight. [8]

The incidence of neonatal sepsis in at term infants with normal birth weight is 0,1% but can increase to 10% in very low birth weight infants, to 35% in extremely low birth weight infants, and up to 50% in infants with birth weight <750 grams. The immune system in infants is strongly influenced by the supply of antibodies from the mother. In very low birth weight infants, maternal antibody concentrations only reach 10-20% of the concentration in at term infants. This low antibody count may cause less protection from pathogens.[20,21]

Low birth weight infants especially those with intra uterine growth restriction have higher risk develop bacterial infections due to a deficiency in the humoral dan cellular immune. Hayashi study in 2020 in Japan which analyzed the differences in DNA methylation between LBW infants and normal birth weight infants, stated that low birth weight infants experienced epigenetic modifications related

to the regulation of immune system and cell maturation. This study found that there were several modifications, such as: modification of macrophage differentiation, modification of mitochondrial apoptosis, modification of nucleotide-excision repair, negative regulation of the inflammatory response, and ovarian cumulus expansion. Increased HUS-1 methylation in low-birth-weight infants causes DNA damage that occurs during DNA replication. Low birth weight infants are very potentially associated with cell metabolism disorders in their life.[23]

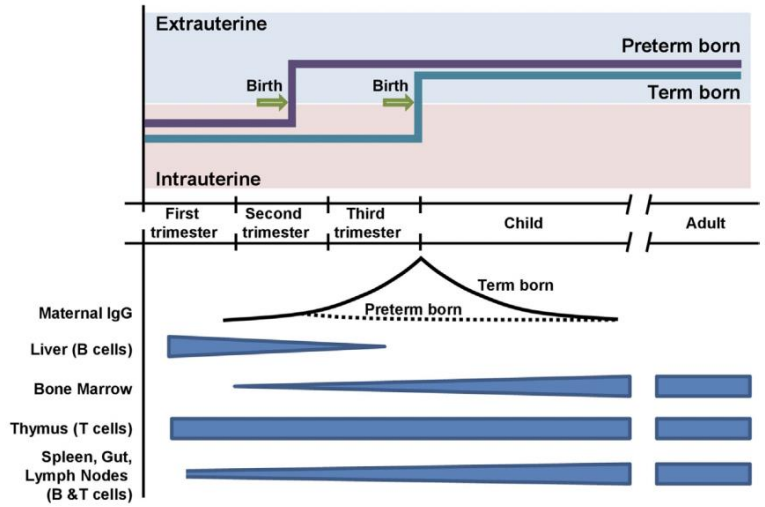

Figure 1. Development of Leukocytes from Early Life to Adulthood in Preterm and At Term Infants.[21]

Conclusions

Pre term infants and low birth weight infants are particularly susceptible to neonatal sepsis. There are many risk factors that influence the occurrence of sepsis in pre term and low birth weight infants. Analysis of the data in this study showed that there was an association between gestational age and birth weight with the incidence of neonatal sepsis at Ulin Hospital Banjarmasin, January-December 2021, that the incidence of neonatal sepsis was associated with preterm and low birth weight infants.

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