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Original Article

The risk of early-onset neonatal sepsis in preterm infants with maternal histologic chorioamnionitis

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ABSTRACT

Background Chorioamnionitis, usually a subclinical condition, may cause preterm delivery and long-term morbidity.

Objective The objective of this study was to determine the risk of early-onset neonatal sepsis in preterm infants with maternal histologic chorioamnionitis (HCA).

Methods This was a prospective cohort study of preterm infants born at Sanglah Hospital, Denpasar from September 2002 to February 2004. Histopathological examinations of the subjects' placentas were done and the infants were monitored for 72 hours for clinical signs of early-onset neonatal sepsis. Maternal and neonatal risk factors were analyzed using multivariate statistical analysis.

Results Eighty-two preterm infants were included, of which 41 were positive for maternal HCA. Twenty-five (61%) of the infants positive for maternal HCA developed early-onset neonatal sepsis, compared to 5 (12%) of those negative for maternal HCA (RR=5, 95%CI 2.12;11.78). Nine infants died from early onset neonatal sepsis. Eight of them had positive HCA, and only one had negative HCA. The average length of hospital stay between infants with and without maternal HCA did not differ significantly [12.0 (SD 5.08) vs. 12.6 (SD 1.34); P=0.80]. Logistic regression model analysis identified only HCA as a significant risk factor for early-onset neonatal sepsis (OR=6.9, 95%CI 2.0;23). Gestational age (OR=1.3, 95%CI 0.8;2.0), birth weight (OR=1.0, 95%CI 0.9;1.0), and neonatal asphyxia (OR=1.0, 95%CI 0.1;4.4) were not found to be significant risk factors.

Conclusion Preterm infants with maternal histologic chorioamnionitis are at a higher risk for developing early-onset neonatal sepsis **[Paediatr Indones 2005;45:160-165].**

Keywords: *maternal histologic chorioamnionitis, preterm, early-onset neonatal sepsis*

Preterm birth is still a national problem, causing more than 70% of neonatal deaths not due to congenital malformation.[1] In Indonesia, the incidence of preterm birth is more than 10%, while in developed countries the incidence is 5-10%.[1] In 2002, the incidence of preterm birth at Sanglah Hospital, Denpasar was 4.7%.[3] Two-thirds of spontaneous deliveries were associated with infection, ischemia, and immune response on chorioamniotic and decidual tissues.[2]

Chorioamnionitis is an acute inflammation of the fetal membranes, clinically diagnosed in 0.5-10.5% of all pregnancies.[7] Early diagnosis is important considering the associated increased risk for maternal and neonatal morbidity and mortality.[8] Since amniocentesis is invasive and amniotic fluid culture time consuming, microscopic histological findings of polymorphonuclear leukocytes in placental tissue has assumed a role in the diagnosis of acute intrauterine inflammation.[9] Spontaneous preterm delivery is one of the

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complications of histologic chorioamnionitis (HCA), occurring in about 70% of all pregnancies. Chandra[11] found that 69.7% of spontaneous preterm deliveries were associated with HCA, while Smullian *et al*[12] found that HCA was associated with an earlier delivery and increased possibility of neonatal sepsis.

This study was conducted to determine the risk of early-onset neonatal sepsis in preterm infants with maternal histologic chorioamnionitis (HCA). The characteristics, length of hospital stay, and mortality of the patients were also studied.

Methods

After approval by the Ethics Committee of Sanglah Hospital/Medical School, Udayana University, this prospective cohort study was conducted in the Intensive Care Unit of Sanglah Hospital from September 2002 to February 2004. The subjects were preterm infants born spontaneously at 28 to <37 weeks' gestation, singleton, live births, with no apparent medical or anatomical uterine abnormality. The exclusion criteria were major congenital anomalies, traumatic deliveries, invasive procedures during delivery, prolonged labour, premature rupture of membranes (PROM), maternal fever (>38°C), recurrent abortion, maternal antibiotic and/or steroid use, and refusal to participate.

Sample size was calculated based on the assumption that the incidence rate of early onset neonatal sepsis in preterms with maternal HCA was 60.9%.[12] The minimum sample size needed was 41 infants in each group ($\alpha = 0.05$; power 80%).

Subjects were recruited by consecutive sampling. After delivery, specimens from the amniotic and chorionic membranes of the placenta were taken on three sites: (1) in a part of the rupture (2-3 cm from the rupture); (2) three centimetres from the base of the umbilical cord; and (3) parts of maternal and fetal tissue 3-4 cm from the umbilical insertion. The specimens were washed with saline solution then fixed in 10% neutral buffered formaldehyde, embedded in paraffin, and stained with haematoxylin-eosin. This procedure was done by residents of obstetrics-gynecology. Identification of HCA was performed in the Anatomical Pathology Department of the hospital. HCA was diagnosed when the pathologist found ≥10 polymorphonuclear neutrophil leukocytes in at least one high-power field (400X) by light microscopy.[9] The pathologist was blinded to clinical findings.

Infants with positive histological examination (HCA+) were put in group I, while those with negative results (HCA-) were assigned as group II or control group. Each group consisted of 41 subjects. After the required sample size was reached, other specimens were kept but not analyzed. If an infant was withdrawn or discharged before a diagnosis of early-onset neonatal sepsis could be established, then he/she would be substituted with another subject with the same histological findings. Both groups were followed for 72 hours after birth, since the definition of early-onset neonatal sepsis was the occurrence of signs and symptoms of clinical sepsis within 72 hours after birth.[14] The diagnosis of clinical sepsis was based on the criteria of Yu and Monintja and established by pediatric residents, who were blinded to histological examination results. The relevant data were collected by chart review. Perinatal asphyxia was defined as Apgar score <7 in the first minute.[15] Low birth weight (LBW) was defined as body weight <2500 grams at birth.[16] Gestational age was determined based on the mothers' last menstrual period or by Dubowitz/Finnstrom scores.

Data were analyzed using SPSS 11.5 for Windows. The univariate association of HCA factor with early onset neonatal sepsis was approximated by determining the relative risk for cohort studies. The chi-square test for nominal variables and Student's t-test for continuous variables were used. Statistical significance was set at $P<0.05$. Ninety-five percent confidence intervals (95%CI) for odds ratios were calculated. Maternal and neonatal factors were examined by logistic regression to determine the best model that would predict early onset of neonatal sepsis.[17]

Results

Ninety-one preterm infants were eligible. Nine of them were not analyzed because the sample size had reached 41 preterms for each group. Twenty-five (61%) of the infants positive for maternal HCA developed early-onset neonatal sepsis, whereas 5 (12%) of those negative for maternal HCA developed it. Nine died due to sepsis; 8 (32%) from HCA+ group and 1 (20%)

Table 1. Univariate analysis of the association between possible risk factors with HCA

Variable	HCA + (n = 41)	HCA - (n= 41)	P
Infant			
Sex			
Male, n (%)	26 (55)	21 (45)	0.264
Asphyxia, n (%)	16 (73)	6 (27)	0.013
Mean birth weight (SD; in grams)	1913.4 (390.2)	2174 (266.2)	0.001
Mother			
Mean age (SD; in years)	25.9 (5.3)	28.3 (5.8)	0.054
Nulliparity, n (%)	26 (63)	19 (47)	0.120
Mean gestational age (SD; in weeks)	32.8 (2.3)	34.3 (1.4)	0.001

HCA = Histologic chorioamnionitis

Table 2. Distribution of early-onset neonatal sepsis by HCA status

HCA	Early-onset neonatal sepsis		Total	RR (95%CI)
	Present (%)	Absent (%)		
(+)	25 (61)	16 (39)	41 (100)	5.0
(-)	5 (12)	36 (88)	41(100)	(2.122;11.78)
Total	30 (36)	52 (64)	82 (100)	

Table 3. Logistic regression analysis of risk factors associated with clinical early-onset neonatal sepsis

Covariate	B	P	OR	95% CI
Gestational age	0.303	0.161	1.354	0.887;2.068
Birth weight	0.002	0.193	1.002	0.999;1.005
Perinatal ssphyxia	-2.58	0.772	0.772	0.134;4.447
HCA	1.937	0.002	6.936	2.072;23.215

B=logistic regression coeffcient

from HCA- group. There were no drop-outs or deaths before 72 hours postnatally. The mean length of stay were not different between the two groups [12.0 (SD 5.08) vs. 12.6 (SD 1.34); P=0.80].

Table 1 shows results of univariate analysis of the association between several maternal and neonatal with maternal HCA. Factors significantly associated with maternal HCA were lower birth weight, perinatal asphyxia, and earlier gestational age at delivery; gender, maternal age, and parity were not significant.

Table 2 shows the distribution of early-onset neonatal sepsis among infants with and without HCA. A significantly higher proportion of infants with neonatal sepsis was found among those with HCA (P=0.001, RR=5.0, 95%CI 2.122;11.781).

Logistic regression analysis was used to determine the association of various factors with early-onset neonatal sepsis independently of confounding factors (**Table 3**). After adjustment for variables significantly associated with early-onset neonatal sepsis in univariate analysis or in the literature, only maternal HCA (P=0.002, OR=6.9, 95%CI 2.072;23.215) remained significantly associated with early-onset neonatal sepsis.

Discussion

Histopathological changes in the placenta can be analyzed *in utero* for diagnosis of chorioamnionitis or early-onset neonatal sepsis.[9,12] Early-onset neonatal sepsis in preterm infants suggests that the fetal inflammatory response syndrome (FIRS) may be elicited by intrauterine infection.

FIRS is a subclinical condition originally described in fetuses presenting with preterm labor, de-

fined as fetal plasma IL-6 concentration greater than 11 pg/ml.The tissue damage causes biochemical, physiologic, and immunologic changes in the host, i.e., C-reactive protein production and activation of T-cells and natural killer cells.[19] The association of HCA with neonatal infection is based on positive culture of placenta and increased risk for perinatal death.[20] Russel *et al*[21] found a higher rate of early mortality when HCA was present in a preterm birth.

In our study, the occurrence of clinical early-onset neonatal sepsis in preterm infants with maternal HCA+ was 61%. Smullian *et al*[12] in their study of 139 pregnancies found 86 (61.9%) cases of HCA associated with an earlier gestational age and possible neonatal sepsis (60.5%). Saling[18] reported the signs of infection among 76% of preterm delivery and birth weight of <2000 grams.

In our prospective study of 82 infants born before 37 weeks gestation, with univariate analysis risk factors such as HCA, earlier gestational age, lower birth weight and perinatal asphyxia were found to be significantly associated with early onset neonatal sepsis. Yancey *et al*[22] found a significant association between early onset neonatal sepsis and earlier gestational age, while Soman *et al*[23] obtained a significant association between early onset neonatal sepsis with birth weight of <2500 grams and 5-minute Apgar score of <7.

Multivariate logistic regression analysis of our data confirmed the association of clinical early-onset neonatal sepsis with HCA (OR 6.9, 95%CI 2.0;23.0). However, earlier gestational age (OR 1.3, 95%CI 0.8;2.1), lower birth weight (OR 1.0, 95%CI 0.9;1.0), and perinatal asphyxia (OR 0.7, 95%CI 0.1;4.4) were not associated with early-onset neonatal sepsis in the logistic regression analysis. In a case-control study, Korbage de Araujo *et al*[24] found that risk factors associated with neonatal infection were inflammatory lesions of the placenta, low Apgar score, and prematurity. Beebe *et al*[25] also found an association between HCA and low one-minute Apgar score and the clinical diagnosis of neonatal sepsis. Our study differed from the above studies in that perinatal asphyxia was defined as first-minute Apgar score of <7 and we did not investigate the influence of severe asphyxia. In a retrospective study, Martius *et al*[26] defined risk factors for early onset neonatal sepsis and found an association between premature rupture of membranes, HCA, and probable neonatal sepsis. Inflammatory lesions of the umbilical cord showed high specificity (92%) and negative predictive value (84%) for diagnosis of neonatal infection. In our study, infants with history of premature rupture of membranes were excluded because it was considered a risk factor that induced preterm labor.

Clearly, HCA is associated with preterm delivery and early-onset neonatal sepsis. For prevention of the intrauterine infection in mother and infant, some studies recommended giving prophylactic antibiotics to mothers who had bacterial vaginosis and preterm labor as risk factors. Trials on prenatal treatment for the prevention of preterm delivery have focused on bacterial vaginosis. Treatment with oral antibiotics of women with previous preterm delivery who had bacterial vaginosis diagnosed in the second trimester resulted in a significant reduction in the incidence of preterm delivery.[27-31] However, treatment in women with intact membranes did not delay or reduce the risk of preterm delivery.[32]

The Centers for Disease Control and Prevention (CDC)[33] recommended two strategies for preventing early neonatal sepsis due to Group B *Streptococcus* (GBS) by giving prophylactic antibiotics to women with preterm labor, with good results. There had been no report whether prophylactic antibiotic is beneficial in preventing early onset neonatal sepsis in preterms with maternal HCA+. Vellaphi *et al*[34] reported that prophylactic antibiotics given to mothers and infants with risk factors reduced the occurrence of early onset neonatal sepsis by as much as 76%.

Although our study showed a significant difference in the risk of early onset neonatal sepsis between preterm infants with HCA+ compared to HCA-, we have to admit several limitations of this study. The diagnosis of HCA was done only by one pathologist. Moreover, we did not perform culture of the placenta or blood from our subjects; the diagnosis was based solely on clinical signs.

We conclude that maternal HCA is a risk factor for early-onset neonatal sepsis in preterm infants. We recommend considering the administration of antibiotics to preterm infants born to mothers with positive HCA immediately after birth.

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