ORIGINAL ARTICLE

Risk Factors for the Development of Hyaline Membrane Disease in Preterm Infants

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ABSTRACT Hyaline membrane disease (HMD) is a respiratory disease commonly found in preterm infants. While this disease occurs as the result of surfactant deficiency which is a function of gestational age, certain maternal and neonatal factors play a role in the development of the disorder. Preterm infants born at the Department of Obstetrics and Gynecology, Cipto Mangunkusumo Hospital, Jakarta, between, March 1997 and May 1998 were studied for the development of HMD. It was concluded that antepartum hemorrhage, gestational age, sex, mode of birth, and the first minute Apgar score were associated with the development of HMD, while the use of contraceptives, early rupture of the membrane, maternal morbidity, and passive cigarette smoking were not. **[Paediatr Indones 1998; 38:243-254].**

Introduction

Hyaline membrane disease (HMD) is one of the most challenging problems in neonatal period both in developing and in industrial countries.[1] This disease is the leading cause of perinatal morbidity and mortality. It is estimated that in Indonesia alone, not less than 150,000 prematurely born babies suffer from neonatal respiratory distress syndrome each year, most of them due to HMD.

Several maternal and neonatal factors are known to influence the development of HMD in preterm infants. Since the cause of HMD is surfactant deficiency, factor that consistently associated with the development of HMD is gestational age. The younger the gestational age, the higher the possibility of an infant to suffer from HMD. In term infants, the incidence of HMD is 0.01%, while in infants less than 30 weeks of gestational age, the incidence is approximately 30%.[1,2] Other risk factors include sex (male to female ratio = 1,5 to 2:1), asphyxia, history of previous HMD, antepartum bleeding,

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twins, cesarean section, maternal diabetes,[3-5] and race.[6-9] On the other hand, maternal illness causing chronic fetal distress, such as hypertension or eclampsia, may have a protective effect for the development of HMD. Similarly, premature rupture of the membrane, especially rupture before the initiation of delivery process, may decrease the incidence of HMD.[7] Some of the risk and protective factors are still controversial and have not been confirmed in Indonesian medical literature. This study aimed to determine the risk and protective factors for the development of HMD in preterm infants delivered in a tertiary hospital.

Methods

This was the first part of larger study on clinical epidemiology and cardiovascular patho-physiology of preterm infants with HMD. This cross sectional study was performed from March 1987 to May 1988. They were followed until developed HMD or not.

Subjects were selected by consecutive sampling method. Since logistic regression model was planned in the final analysis, estimation of the number of study subjects was calculated by using Hsieh's formula.[10] With $\alpha = 0.05$; β 0.20, and the chosen significant odds ratio (OR) of 2, and correlation amongst independent variables was estimated to be 0.30, then 312 subjects were required.

All neonates born at the Department of Obstetrics and Gynecology, Cipto Mangunkusumo Hospital with the gestational age of less than 37 completed weeks were included in the study. The following eligible subjects were excluded from the study: (1) twins, (2) clinical evidence of congenital anomaly except patent ductus arteriosus, (3) parents disagreed to be included in the study.

Clinical data were collected by the author or residents in pediatrics, Department of Child Health, Medical School, University of Indonesia, Jakarta. Maternal variables collected included age, number of pregnancy and delivery, history of abortion, use of contraceptive, use of medication during pregnancy, history of antenatal care, pregnancy morbidity, and history of previous premature delivery. Mode of delivery, reason for operative delivery, clinical presentations and relevant laboratory results were also collected. Data of infants included sex, birth weight, complete physical examination, gestational age, Apgar scores in the first and 5th minutes, resuscitation needed, and relevant laboratory results were collected.

Determination of risk or protective factors for the development o HMD was performed in 2 steps. First, univariate analysis was performed of each of the risk factors, by using independent t-test or chi-squared test. Thereafter, a multivariate analysis (logistic regression model) was performed, with the risk factors as the independent variables, and HMD as the dependent variable. For all hypothesis testing, $p<0.05$ (2-tailed test) was considered significant.

Results

During the period of March 1997 until May 1998, 314 neonates of less than 37 weeks gestational age who registered at the Department of Obstetrics and Gynecology met the study criteria. In that period there were 4882 live births, giving the prevalence of prematurity of 6.43%. Six out of those 314 preterm neonates (or 3 pairs) were excluded because of being twins.

Subject characteristics

All neonates were delivered at the Department of Obstetrics and Gynecology, Medical School, University of Indonesia / Cipto Mangunkusumo Hospital, Jakarta. Three hundred and eight neonates with their mothers were registered. The maternal age ranged between 16-43 years old (mean 26.2, SD 5.97 years). The number of pregnancy ranged between 1-7 (mean 3.4) while the number of delivery ranged from 1-6 (mean 3.2). Most of the mothers (186) delivered spontaneously, 99 through cesarean section. Most mothers did not perform antenatal care, and 270 had no illness during their pregnancy. Table 1 shows characteristics of the mothers.

Amongst the 308 neonates, 167 were male (54.2%), and 141 female (45.8%). The gestational age ranged between 26-37 weeks (mean 31.7). The birth weight ranged from 650-2680 grams (mean 1624.6). The first minute Apgar score ranged from 1-9 (mean 6,8), and in 5th minute Apgar score was 5-10 (mean 9.3). Table 2 shows characteristics of the neonates.

Relation between risk factors and the incidence of HMD

A two-step analysis was performed to evaluate various risk factors on mothers or neonates on the occurrence of HMD. First, univariate analysis was performed to look for the association between each risk factor in mothers and neonates towards the occurrence of HMD. In this level, the association between one risk factor with HMD was calculated by ignoring the confounding factors. Therefore, when there was an association, it might not be a cause-effect relationship. The second step is performing multivariate analysis. In doing so, risk factors that gave significance in the univariate analysis were analyzed simultaneously; these were added with risk factors that theoretically relevant with the development of HMD although it could not be proven significantly in univariate analysis. This analytical approach could exclude confounding factors which mean that if ever a relationship was found between one independent variable (risk factor) with the occurrence of HMD, it should have been a cause-effect relationship. With this analysis, the role of each risk factor against the incidence of HMD could be explained. The analysis that met the data (dichotomous nominal dependent variable, and nominal and numeric scale independent variables) was logistic regression model.

Table 1. Clinical characteristics of mothers (N=308)

Characteristics		Total	Percentage
Age group (year)	15 - 19	44	14.3%
	20 - 24	82	26.6%
	25 - 29	93	30.2%
	30 - 34	51	16.6%
	35 - 39	31	10.0%
	40 -	7	2.3%
Number of pregnancy	1	44	14.3%
	2 - 4	196	63.6%
	5 -	68	22.1%
Number of delivery	1	36	11.7%
	2 - 4	207	67.2%
	5 -	65	21.1%
Use of contraceptive before last pregnancy	None	214	69.4%
	Pill	34	11.2%
	Injection	38	12.3%
	Implant	3	1.0%
	IUD	14	4.5%
	Others	5	1.6%
Active smoker	None	302	98.1%
	Yes	6	1.9%
Passive smoker	None	137	44.5%
	Yes	171	55.5%
Illness during pregnancy	Denied	270	87.7%
	Bleeding	16	5.2%
	Hypertension	18	5.8%
	Others, incl. diabetes	4	1.3%
Mode of delivery	Spontaneous	186	60.4%
	Cesarean section	99	32.1%
	Vacuum extraction	12	3.9%
	Forcipal extraction	5	1.6%
	Others	6	2.0%

Table 2. Distribution of characteristics of preterm infants (N=308)

Characteristics		Total	Percentage
Gender	Male	167	54.2%
	Female	141	45.8%
Gestational age (week)	25 - 29	51	16.6%
	30 - 34	226	73.4%
	35 - 37	31	10.0%
Birth weight (gram)	500 - 999	31	10.0%
	1000 - 1499	75	24.4%
	1500 - 1999	133	43.2%
	2000 - 2499	64	20.8%
	2500 -	5	1.6%
1st minute Apgar score	1 - 3	25	8.1%
	4 - 6	92	29.9%
	7 - 10	191	62.0%
5th minute Apgar score	4 - 6	8	2.6%
	7 - 10	300	97.4%

Univariate analysis

Analyses for the relationships between the incidence of HMD (dependent variable) with risk factors (independent variables) were performed towards each variable, namely (1) maternal age, (2) use of contraceptive (did not participate, hormonal, non-hormonal contraceptive), (3) passive cigarette smoking, (4) pregnancy morbidity (none, hypertension, other), (5) antepartum hemorrhage, (6) duration of fetal membrane rupture (<6 hours, 6-11 hours, 12-23 hours, > 24 hours), (7) mode of delivery (spontaneous, cesarean section, other), (8) sex, (9) gestational age, (10) birth weight, and (11) first minute Apgar score.

It is important to note that the risk factors that we have been looking for were the risk factors for the development of HMD in preterm infants, and not the risk factors for the occurrence of preterm delivery. That was why factors that had been known to have effect on the incidence of prematurity but did not play a role in the development of HMD (e.g., primigravida, history of premature delivery, matenal nutritional status, history of antenatal care, socioeconomic status, unwanted child, marriage history, etc.) were excluded from independent variable group.

For characteristics with numeric scale, an independent t-test was used to compare those of the HMD and non-HMD groups. For nominal scale variables, an x^2 test was used for hypothesis testing. The number of pregnancy, number of delivery, the 5th minute Apgar scores were not included both in univariate and multivariate analyses because there were no theoretical basis. Active smoking was also excluded from analysis, because the number of mothers who were active smokers was small (6 out of 308 mothers). Table 3 shows the results of univariate analysis. There was a significant association between the occurrence of HMD with maternal morbidity, antepartum hemorrhage, mode of delivery, gender, gestational age, birth weight, and one minute Apgar score. On the other hand, maternal age, use of contraceptive, passive smoking, and fetal membrane rupture had shown no association with the occurrence of HMD.

Logistic regression analysis

Logistic regression analysis was used to explain the relationship between each independent factor with HMD, after excluding the confounding factor. The dependent variable was the occurrence of HMD, whereas the independent variables including factors from maternal and the neonates.

Table 3 shows that the independent variables that had a significant association with the development of HMD were maternal morbidity, antepartum bleeding, mode of delivery, gender, gestational age, birth weight, and one minute Apgar score. On the other hand, maternal age, participation in family planning, passive cigarette smoking, and duration of fetal membrane rupture had no association with HMD. Nevertheless, those independent variables were still put into logistic regression analysis, because it had not been explicitly proven that they had no association with HMD, and because negative result in univariate analysis might be caused by one or more confounding factors.

In order to include independent variables into logistic regression analysis, the multicollinearity, that was a highly correlation between 2 independent variables, should be excluded. For that reason, a matrix correlation analysis was needed. If there is a high correlation between two independent variables (r=0.8, or more), only one of them had to be chosen, or a new independent variable developed, because both variables basically represented the same concept. The correlation matrix shows that there was a high correlation between gestational age and birth weight (r=0.9288); in this case, gestational age was chosen as an independent variable, because HMD is due to surfactant deficiency which highly associated with gestational age. Therefore, the independent variables that were included as the potential risk factors were: (1) maternal age, (2) use of contraceptive, (3) passive smoking, (4) pregnancy morbidity, (5) antepartum bleeding, (6) duration of fetal membrane rupture, (7) mode of delivery, (8) gender, (9) gestational age, (10) the one minute Apgar score. Logistic regression analysis was done by using *SPSS for Windows Release 6.0*, using backward stepwise method and Wald statistic. Initially, all independent variables were put into the model.

Table 3. Univariate analysis shows the relationship between independent variables with the occurrence of HMD

	Characteristics	HMD (n=87)	Non- HMD (n=221)	Hypothesis testing or odds ratio*
Mother age (year)	Mean	27.04	25.93	p =0.139
	SD	6.28	5.83	
Family planning	None[R]	57	157	p = 0.716; OR = 1.38 (0.75; 2.52)
	Hormone	25	50	p = 0.268
	Non-hormone	5	14	OR = 0.98 (0.29; 3.10); p = 0.976
Passive smoker	No[R]	51	120	OR = 1.19 (0.70;2.04)
	Yes	36	101	p =0.492
Pregnancy morbidity	None[R]	64	206	
	Hypertension	11	7	p = 0.000; OR = 5.06 (1.73; 15.17); p = 0.000; OR = 4.83 (1.74; 13.62);
	Bleeding & other	12	8	p = 0.000
Antepartum bleeding	Yes	16	20	OR =2.26; (1.04; 4.91); p = 0.022
	No[R]	71	201	
Duration of fetal membrane rupture	<6 hour[R]	57	138	p = 0.593; OR = 0.62 (0.27; 1.40);
	6-12 hour	10	39	p = 0.216; OR = 1.01 (0.29; 3.28);
	12-24 hour	5	12	p = 0.987; OR = 1.13 (0.54; 2.37);
	>24 hour	15	32	p = 0.718
Mode of delivery	Normal[R]	40	146	p = 0.015; OR = 2.18 (1.23; 3.86).
	Cesarean section	37	62	p = 0.004; OR = 281 (1.05; 7.48);
	Others	10	13	p = 0.020
Sex	Male	61	106	OR = 2.55 (1.44; 4.50);
	Female[R]	26	115	p =0.000
Gestational age (week)	Mean	30.54	32.16	p = 0.000
	SD	2.21	2.5	
Birth weight (gram)	Mean	1412.8	1707.9	p = 0.000
	SD	438.13	420.72	
The 1st min. Apgar score	Mean	5.20	7.38	p = 0.000
	SD	1.72	1.72	

[R] = reference value, e.i. OR (odds ratio) = 1. Numbers in bracket indicate 95% confidence intervals.

Then one by one the computer excluded those variables with no significant result, until only the ones with significant result were left. The complete model of logistic regression was depicted in Table 4; this shows a significant relationship between HMD and antepartum hemorrhage, mode of delivery, gender, gestational age, and the first minute Apgar score. On the other hand, maternal age, passive smoker, pregnancy morbidity, and use of contraceptive did not associate with the development of HMD.

Table 4. Results of logistic regression analysis with the maternal and neonatal factors as independent variables and occurrence of HMD as dependent variable

Var	B	SE	Wald	Df	Sig	R	Exp (B)
Pregnancy hemorrhage (1)	0,4405	0,2439	3,2623	1	0,0709	0,0587	1,5534
Gestational age	-0,4217	0,0822	26,3243	1	0,0000	0,2576	0,6559
Mode of birth			8,2875	2	0,0159	0,1081	
• Birth (1)	0,2711	0,2725	0,9903	1	0,3197	0,0000	1,3114
• Birth (2)	0,4016	0,3869	1,0779	1	0,2992	0,0000	1,4943
Sex (1)	0,3390	0,1752	3,7452	1	0,0530	0,0690	1,4035
First minute Apgar score	-0,7618	0,1021	55,6584	1	0,0000	0,3825	0,4668
Constant	17,5896	2,8426	38,2902	1	0,0000		

Discussion

Before discussing the study results, it is necessary to discuss the validity and reliability of gestational age determination. Determining the neonate's clinical gestational age always invite a controversy.[5] Roberton stated that determining the gestational age by clinical examination was unnecessary because it should be easily obtained by knowing the first day of the last menstruation. What was needed was to make sure that the mother did not miss calculating her last menstrual period,[5] except for those with unpredictable menstrual cycle. This statement should be cautiously implemented in Indonesia, bearing in mind that there are still a lot of low educated mothers who often forget or not paying attention to her menstrual cycle. The latest accurate method to determine the gestational age is by ultrasound examination performed by an experienced ultrosonographer.[5] Whatever method is chosen there is a chance for inaccuracy about 2 weeks compared to ultrasound examination.[11] Dubowitz or Ballard methods, which are often used in practice to determine the neonatal gestational age using physical and neurological criteria, are difficult to use in preterm infants, especially those who are sick (for example asphyxia).

In this study the gestational age was determined by using Dubowitz[12] method and by calculating from the first day of the last menstruation. If there was any doubt then a review was performed by two or more doctors.

Risk factors of HMD in preterm infants

Some of this study results confirmed previous results, and some were not in accordance to today's knowledge. From the univariate analysis it was proven that maternal morbidity, antepartum bleeding, delivery method, gender, gestational age, birth weight and the first minute Apgar score had a significant association with the incidence of HMD. On the other hand, maternal age, use of contraceptive, passive cigarette smoking, and the duration of fetal membrane rupture had no significant association with the incidence of HMD.

Maternal age has been known as one of the risk factors in HMD incidence. From both univariate and multivariate analyses, no significant association was found between maternal age and the incidence of HMD. Maternal age has an association with premature delivery,[13] but does not have any association with the incidence of HMD in preterm infants.

Use of contraceptives was included as one of the risk factor to determine association between exposure to hormone in early pregnancy with lung development, especially the production of surfactant. Based on that fact, those who take part in family planing were divided into hormonal (pill, injection, implant) and non-hormonal groups (IUD, condoms, calendar system). In other subject, exposure to hormone in early pregnancy can develop into congenital disorders including extremities and heart anomalies, although this is still contoversial.[14] Using hormone for a long time which effect was still exists when the mother become pregnant might have caused the exposure, Sometimes the mother, during the early stage of her pregnancy, did not realized that she was pregnant and those who use pills still consume the pills for several days or weeks more. In this study the exposure to hormone latter in the pregnancy did not have any association with the incidence of HMD. Indirectly this mean that exposure of maternal hormone did not interfere with lung development in association with the production of surfactant.

Passive cigarette smoker is included into risk factor based on report that stated that exposure to cigarette smoke would cause intrauterine growth retardation, such has been proven by low birth weight neonates born from smoking mothers.[15] Passive exposure to cigarette smoke would also had the same results but in a milder degree. On the other hand it had been assumed that lengthy stress in utero would accelerate the development of surfactant. such as heroin addicted mothers or mothers with high blood pressure.[5] This study did not support that statement, in other words, passive smoke did not have association with HMD incidence. It had to put forward the fact that data about passive smoker was not traced carefully and based only on the interview without asking in details about the nature and degree of exposure.

Mode of delivery posed as a strong risk factors in the incidence of HMD in preterm infants. In some cases, especially those with the history of cesarean section due to difficult delivery process, the incidence of HMD might had been cause by asphyxia

(asphyxia as confounding factor). But in this series, no strong association was found between mode of delivery and asphyxia. The logistic regression analysis done to those factors (mode of delivery and 1st minute Apgar score) showed that both factors were independently posed as risk factors in the incidence of HMD.

Contrary to the present knowledge, this study did not find a relationship between the incidence of HMD and the duration of the rupture of the membrane. In the literature, it is said that early rupture of the membrane, especially before the delivery process begins, is associated with the decreased incidence of HMD.[5] It is assumed that rupture of the membrane accelerates surfactant production, which would act as a protective factor towards in preventing the incidence of HMD in preterm infants.

In logistic regression analysis, it seems that the lowest odds ratio is the Apgar score, i.e., 0.47 (it would have become 2.13 when the reference had been changed from the highest to the lowest). This proved that the 1st minute Apgar score plays an important role in the incidence of HMD in preterm infants. Because the presence of HMD was scored 0 and non-HMD scored 1, and 8 minute Apgar score served as the reference value, the odds ratio value of 0.47 means that if the Apgar score raises 1 unit, the probability of HMD will decrease more than 2 times, as long as the other independent variables were constant.

The second highest odds ratio was antepartum bleeding, i.e., 1.55. It means that the presence of antepartum hemorrhage will increase the incidence of HMD 1.5 times, as long as the other variables stay constant. In the univariate analysis the odds ratio was 2.26 which mean that there was a confounding factor in this series that would looked as if the antepartum hemorrhage had a strong association with the incidence of HMD. The same thing was seen in the cesarean section (odds ratio 2.31 in univariate analysis and 1.31 in logistic regression), mode of delivery (2.81 vs 1.49) and gender (2.55 vs 1.40).

Maternal morbidity, in univariate analysis showed a very significant association with the incidence of HMD (odds ratio 5.66 and 4.83, p=0.000), but it did not fit the multivariate model. This shows that maternal morbidity served as a confounding factor for other variables. In multivariate analysis, the confounding factors were controlled, so that no significant association was found. It is important to remember that maternal morbidity did not include antepartum hemorrhage which stood as a separate risk factors. Diabetes mellitus is known as a risk factor for HMD, while hypertension, including pre-eclampsia and eclampsia are protective factors.[7] The fact only few mothers suffered from those diseases might had caused this negative result. Only 18 mothers suffered from hypertension and 2 from diabetes.

Then a question on which variables confounded by maternal morbidity would come up? Through *post-hoc analysis* that was performed by investigator-selected variables technique, it seemed that maternal morbidity is a confounding factor towards the first minute score of Apgar. The analysis was performed, firstly, by putting maternal

morbidity variables as the only independent variables in logistic regression model. As long as the Apgar score of the first minute excluded from the model, maternal morbidity has it's significance. But when the score was included, then no significance was found. Interaction analysis between independent variables also gave the same conclusion. This stresses the importance of multivariate analysis as a cause-effect association, if the causal variables or the risk factors were more than one.

Gestational age, although represented the main determinant in the occurrence of surfactant deficiency, only gave the odds ratio of 0.66 (or 1/0.66=1.52 if the reference was reversed). This was less than Apgar score of the first minute. Table 4 shows that an increase of gestational age of 1 unit (1 week) would decrease the probability of the development of HMD 1.52 times. Whereas increased score of Apgar in the first minute 1 unit would decreased the incidence of HMD 2.13 times. But range of gestational age (26-37 weeks) is wider than Apgar score range (1-8). So gestational age still an important risk factor in the occurrence of HMD in preterm infants.

This study did not confirm the present of protective factors that is factors that can lessen the probability of HMD in preterm infants. In the literature what was described as protective factors were lengthy fetal membrane rupture, narcotics, maternal diseases that gave stress to the fetus such as hypertension, eclampsia or pre-eclampsia.[13]

Finally, since HMD has a direct relationship to surfactant deficiency, so it is important to discuss the relationship between risk factors in this study to surfactant deficiency. Factor that has direct association with surfactant deficiency is gestational age, because the of surfactant depends on it. Gender is associated with HMD through the role of estrogen in accelerated surfactant maturation.[16,17] It mean that males are more susceptible than female. Neonates that were born by cesarean section suffered less chest compression that will lessen the surfactant release compare to those born naturally. As the consequences, they would have more change of having HMD. Asphyxia (hypoxia and hypercarbia) decreased the production and secretion of surfactant that mean that preterm infants with asphyxia would had more change of having HMD compare to those without asphyxia. The same goes with antepartum bleeding which put fetus in a hypoxic situation that gave obstacle to the production and secretion of surfactant.

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