



Risk factors for respiratory distress syndrome in full-term neonates

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Background: Respiratory distress syndrome (RDS) is a one of the most common cause of respiratory morbidity and mortality in neonates. This study was conducted to investigate the risk factors for RDS in full-term neonates.

Methods: We conducted this retrospective study using medical records. The study group included 80 full-term neonates diagnosed with RDS and hospitalized in the neonatal intensive care unit between January 2012 and December 2016, at Yeungnam University Hospital. We analyzed sex, gestational age, birth weight, delivery method, maternal age, number of pregnancy, history of abortion, and complication of pregnancy. The control group included 116 full-time neonates who were hospitalized with jaundice during the same period.

Results: The incidence of full-term RDS was more common in males (odds ratio [OR], 3.288; 95% confidence interval [CI], 1.446-7.479), cesarean section (OR, 15.03; 95% CI, 6.381-35.423), multiparity (OR, 4.216; 95% CI, 1.568-11.335). The other factors rendered no significant results.

Conclusion: The risk factors for RDS in full-term neonates were identified as male sex, cesarean section, and multiparity. Further studies involving more institutions are needed to clarify the risk factors for RDS in full-term infants.

Keywords: Full-term; Neonatal respiratory distress syndrome; Risk factor

INTRODUCTION

Neonatal respiratory distress syndrome (RDS) is one of the major causes of respiratory failure and neonatal death in premature infants and is caused by a lack of pulmonary surfactant due to fetal lung immaturity. Treatment is the administration of a synthesized pulmonary surfactant, following which the course of the disease markedly improves. According to previous reports, the most important risk factors for RDS are prematurity and male sex [1,2]. In fact, a study comparing the

incidence of RDS in premature infants showed a 45% incidence in premature infants between 23 to 33 weeks; however, the incidence was markedly decreased to 4% and less than 1% in 34-36 weeks and over 37 weeks, respectively [1]. Additionally, other studies have reported an incidence of approximately 10.5% at 34 weeks, 1% at 37 weeks, and 0.3% at 38 weeks [3]. However, in practice, even if a patient is born at full-term, RDS frequently develops, and patients are hospitalized in the neonatal intensive care unit (NICU) for mechanical ventilator and pulmonary surfactant treatment. Condò et al. [4] studied the risk factors of RDS in full-term infants and compared it with those in preterm infants. The report mentioned that risk factors such as male sex, low birth weight, and cesarean section increase the risk of RDS in both preterm and full-term infants, and gestational diabetes and pregnancy-induced hypertension are the risk factors for RDS in late preterm and full-term neonates. However, as far as the author

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knows, there have been no studies regarding this in Korea. Therefore, this retrospective study aims to investigate the risk factors for RDS in full-term infants and to help diagnose and treat RDS.

MATERIALS AND METHODS

1. Patients

This retrospective study was approved by the Clinical Research Ethics Committee of Yeungnam University Hospital (YUMC-2018-10-032). The subjects were divided into an experimental group (full-term infants diagnosed with RDS) and a control group (full-term infants with neonatal jaundice). Risk factors were assessed on the basis of history of hospitalization at the time of admission; we investigated gestational age, sex, birth weight, delivery method, Apgar score, maternal age at delivery, pregnancy frequency, abortion history, pregnancy-induced hypertension, gestational diabetes, preeclampsia, intrauterine growth restriction, premature rupture of membranes, oligohydramnios, polyhydramnios, history of meconium aspiration, placenta previa, placenta abruption.

The study group consisted of 80 full-term infants who were diagnosed with RDS and hospitalized in the NICU of Yeungnam University Hospital, between January 2012 and December 2016. The diagnostic criteria for RDS in full-term infants were as follows [5-8]: (1) full-term infant with gestational age more than 37 weeks; (2) characteristic clinical manifestations (tachypnea, nasal flaring, progressive dyspnea, grunting, cyanosis, chest retraction, and severe respiratory distress requiring positive pressure ventilation); (3) a characteristic finding in the chest radiograph (ground glass appearance, air bronchogram, total white out); (4) decreased oxygen demand after treatment with pulmonary surfactant.

The control group included 116 full-term infants who were admitted with neonatal jaundice during the same period, except for jaundice caused by sepsis or bacterial infection, or hemolytic anemia.

Among them, a history of meconium aspiration was defined as a meconium stained amniotic fluid at the time of birth, or patients with meconium stained umbilical cord or meconium under the fingernail found on physical examination at the time of admission. Intrauterine growth restriction can

result in a baby being small for gestational age (SGA), which is defined as a weight below the 10th percentile for the gestational age. The exclusion criteria were; patients who received pulmonary surfactant therapy before admission to this hospital, and patients with congenital heart disease.

The gestational age was divided into four compartments of 37 weeks, 38 weeks, 39 weeks, 40 weeks, or more, and body weight was divided into five compartments of from 2,000 g to less than 2,500 g, from 2,500 g to less than 3,000 g, from 3,000 g to less than 3,500 g, from 3,500 g to less than 4,000 g and more than 4,000 g. Maternal age was divided into three compartments of 20s, 30s, 40s, and over.

2. Statistical analyses

Data were analyzed using SPSS for Windows ver.10.0 (SPSS Inc., Chicago, IL, USA). Chi-square test was used to check for any significant differences between the two groups, and correlation was analyzed by logistic regression analysis. Statistical significance was considered in case of $p < 0.05$.

RESULTS

The results are as follows (Table 1). (1) RDS occurred more frequently in males (male, 53 [66.3%]; female, 27 [33.7%]; $p=0.018$), the incidence of RDS was 3.288 times higher than that in females ($p=0.005$). (2) In case of the delivery method, cesarean section was more frequent associated with RDS than vaginal delivery (cesarean section, 58 [72.5%]; vaginal delivery, 22 [27.5%]; $p < 0.001$), the incidence of RDS was 15.034 times higher with cesarean section than with vaginal delivery ($p < 0.001$). (3) The mean birth weight was 3,198 g. The frequency of each birth weight was 2,000 g to less than 2,500 g in 3 cases, 2,500 g to less than 3,000 g in 26 cases, 3,000 g to less than 3,500 g in 35 cases, 3,500 g to less than 4,000 g in 12 cases, and 4,000 g or more in 4 cases. (4) The mean age of the maternal age at the delivery was 34.0 years (34.01 ± 3.53). Frequencies in the maternal age categories were follows: 7 in the 20s, 69 in the 30s, and 4 in the 40s. (5) Frequencies in the gestational age categories were as follows: 32 in 37 weeks to 37 weeks 6 days, 34 in 38 to 38 weeks 6 days, 6 in 39 weeks to 39 weeks 6 days, and 8 in over 40 weeks. The highest frequency was at 38 weeks ($p < 0.001$). However,

when logistic regression analysis was performed based on gestational age over 40 weeks, it showed that 37 weeks ($p=0.483$), 38 weeks ($p=0.504$), and 39 weeks ($p=0.739$) were not significant. (6) Depending on which pregnancy was associated with RDS, the frequencies were as follows: 14 (17.5%) in first pregnancy, followed by 29, 25, 9, and 3 in second, third, fourth, and fifth pregnancies, respectively (36.3%, 31.3%, 11.3%, and 3.8%). The incidence of RDS

was markedly low in the primiparous group ($p<0.001$), and the incidence was increased by 4.216 times ($p=0.004$) in pregnancies beyond the second. (7) Based on abortion history: 58 (72.5%) women did not have an abortion history, and 22 (22.5%) women did. This was similar to results of the number of pregnancies, but not statistically significant ($p=0.102$). There was one case where the mother was diagnosed with pregnancy-induced hypertension. There were 2 cases (2.5%)

Table 1. Patient characteristics and analysis of risk factors in two groups (%)

Factor	Case group (n=80)	Control group (n=116)	p-value
Gender			0.018
Male	53 (66.3)	57 (49.1)	
Female	27 (33.7)	59 (50.9)	
Gestational age (wk)			<0.001
37	32 (40)	19 (16.4)	
38	34 (42.5)	48 (41.4)	
39	6 (7.5)	25 (21.6)	
<40	8 (10)	24 (20.7)	
Birth weight (g)			0.301
<2,500	3 (3.8)	1 (0.9)	
2,500-3,000	26 (32.5)	32 (27.6)	
3,000-3,500	35 (43.7)	60 (51.7)	
3,500-4,000	12 (15)	21 (18.1)	
>4,000	4 (5)	2 (1.7)	
Delivery method			<0.001
Vaginal delivery	22 (27.5)	101 (87.1)	
Cesarean section	58 (72.5)	15 (12.9)	
Maternal age			0.103
20s	7 (8.8)	23 (19.8)	
30s	69 (86.3)	87 (75)	
40s	4 (5)	6 (5.2)	
Number of pregnancy			<0.001
Primipara	14 (17.5)	49 (42.2)	
Multipara	66 (82.5)	67 (57.8)	
History of abortion			0.102
With	22 (27.5)	24 (20.6)	
Without	58 (72.5)	92 (79.3)	
Complications of pregnancy			<0.001
PIH	1 (1.3)	1 (0.9)	>0.999
Gestational diabetes	2 (2.5)	1 (0.9)	0.568
IUGR	2 (2.5)	0 (0)	0.165
PROM	3 (3.8)	1 (0.9)	0.306
Oligohydramnios	3 (3.8)	0 (0)	0.066
Meconium stain	9 (11.3)	2 (1.7)	0.008

Values are presented as number (%).

PIH, pregnancy induced hypertension; IUGR, intrauterine growth restriction; PROM, premature rupture of membranes.

each, born to mothers with gestational diabetes and intrauterine growth restriction, respectively. Nine cases (11.3%) of suspected meconium aspiration were noted.

DISCUSSION

In this study, it was found that male sex, cesarean section, and multiparity had a statistically significant association with an increased incidence of RDS.

Prematurity is a typical risk factor for RDS in neonates [1]. However, it is possible for RDS to occur even in full-term infants. In a study by Dani et al. [9], 59,990 infants of 63,537 total newborns were reported to be full-term (at 37 weeks or more) and 53 (0.1%) of the 59,990 full-term infants were diagnosed with RDS. In this study, we did not investigate the incidence of RDS in full-term infants, but we wanted to assess the risk factors.

We confirmed that male sex was one of the risk factors for RDS in full-term infants and this was corroborated by previous studies. The reason is summarized as follows. First, androgen (male sex hormone) regulates the signal transduction pathways of epidermal growth factor and transforming growth factor-beta, delaying the fetal lung maturation. It also delays the secretion of fibroblast-pneumocyte factor, delaying the development of type II alveolar cells, thereby reducing the secretion of the pulmonary surfactant. On the other hand, estrogen (female sex hormone) promotes the synthesis of pulmonary surfactants such as phospholipid, lecithin, surfactant protein A or B, and increases the number of type II alveolar cells by increasing the production of lamellar bodies [10-13].

This study showed that the incidence of RDS was significantly increased with relatively lower gestational age, although it was a study on full-term infants. These results suggest that lower gestational age makes maturation of the fetal lungs slower. However, this finding lacks credibility because the subjects were all 37 weeks or older in this study. Additionally, logistic regression analysis of gestational age at 40 weeks showed that it had no significant effect on the development of RDS. Further research on this subject is warranted in the future.

Cesarean section is known to be an important factor affecting the respiratory difficulties in newborns [14]. In this study, only 12.9% of the control group and 72.5% of the patients

with RDS who were hospitalized, were delivered through a cesarean section; these findings were similar to those of a previous study. Cesarean section is a risk factor for RDS because the fetus absorbs about one-third of the fetal lung fluid during vaginal delivery, whereas proper absorption of fetal lung fluid is not achieved in infants delivered through a cesarean section. In addition, the labor process itself matures the system that makes the surfactant, and this process is omitted in a cesarean section. Hence, the risk of RDS is increased in the infants delivered through a cesarean section [15].

In this study, it was confirmed that more infants born to multiparous women had RDS, thereby confirming multiparity to be a risk factor for the same. This is similar to the results of studies performed by Melamed et al. [16] and Altman et al. [17] published in 2009 and 2013, respectively. However, while those studies were conducted on preterm infants, this study was performed on full-term infants. Despite this difference, both studies have shown that multiparity increases the risk of RDS in neonates. The mechanism is still unclear and further research is needed in this area.

Factors, such as birth weight, maternal age at birth, history of abortion, pregnancy-induced hypertension, gestational diabetes, oligohydramnios, premature rupture of membranes, and intrauterine growth restriction were not found to be directly related to the development of RDS in this study. In a study by Liu et al. [18], premature rupture of membrane and gestational diabetes were found to be important risk factors for RDS in full-term infants; however, this study did not show any significant results. This may be because of a smaller number of patients included in the study and unavailability of a detailed history because most of the experimental newborns in this study were born in other hospitals.

The limitations of this study were as follows. First, high possibility that there was no detailed history available of maternal diseases, medications, premature rupture of membranes, etc. Because most of the hospitalized newborns were born in other hospitals. Second, neonates with severe respiratory distress at the time of hospitalization, who were unable to undergo arterial blood gas analysis at the time of first appearance of symptoms because of early application of artificial respiration including tracheal intubation and rapid use of pulmonary surfactant, could not be included in the study. Third, the representation is low because the study was conducted on patients who were admitted to a single university

hospital. Nine newborns with a history of meconium aspiration were included in the study group and the results were significant in declaring this as a risk factor when compared with the control group ($p=0.008$). However, if meconium stained amniotic fluid at the time of birth, meconium stained umbilical cord, or meconium under the fingernail, is accompanied by dyspnea and the patient has to undergo positive pressure ventilation and pulmonary surfactant treatment, a controversy is likely to arise as to whether the diagnosis should be RDS or meconium aspiration syndrome [19]. This is another limitation of this study as it is difficult to know the precise state of the patient at the time of admission because of its retrospective nature.

In conclusion, the risk factors for RDS in full-term infants were male sex, cesarean section, and multiparity. However, prospective studies involving more hospitals are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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