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Original Research Article

Study on risk factors of respiratory distress syndrome in term neonates: a retrospective case-control study

Sunil B. , E. Nithya, Girish N.*

Department of Paediatrics, KIMS, Bangalore, Karnataka, India

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***Correspondence:**
Dr. Girish N.,
E-mail: drgirish79@gmail.com

ABSTRACT

Background: Respiratory distress syndrome (RDS) is one of the most common causes of neonatal respiratory failure and neonatal death. It is more common in preterm neonates but also been found in term and late preterm neonates. This study aims at studying the risk factors for developing RDS in term neonates. Objectives was to study the maternal and perinatal risk factors for RDS in term neonates.
Methods: This is a retrospective case control study conducted in neonatal intensive care unit of tertiary care centre. A total of 100 term neonates with RDS were taken as cases and 150 normal term neonates were taken as control. Data were collected from the hospital NICU records, maternal and neonatal history was taken. The $\chi 2$ tests or Fisher's exact text were used for one-way risk factor analysis. The effects of multiple factors on term neonatal RDS were analyzed using logistic regression analysis.
Results: In our study RDS in term neonates was significantly associated with following risk factors like selective cesarean section, male sex, SGA, oligohydramnios, MSAF, severe fetal distress, birth asphyxia, PROM, and maternal-fetal infection. Among the significant risk factors severe birth asphyxia, maternal-fetal infection, PROM, MSAF were showing positive association with RDS in full-term neonates.
Conclusions: Several high-risk factors such as severe birth asphyxia, maternal-fetal infection, PROM, and MSAF were closely correlated with full-term neonatal RDS. Hence these could provide a significant reference for the diagnosis and treatment of term neonatal RDS.

Keywords: Full term neonate, High-risk factors, Respiratory distress syndrome

INTRODUCTION

Respiratory distress syndrome (RDS) is one of the most common causes of NICU admission and neonatal death. It is mainly found in premature infants, the risk of developing into RDS increased with decreasing of gestational age and birth weight; the incidence rate is 80% in infants <28 weeks gestation, 60% at 29 weeks, and 15-30% at 32-34 weeks, but declined with maturity to 5% at 35-36 weeks and is almost 0% by 39 weeks gestation.[1] RDS accounted for 6.8% of cases of respiratory distress in term or near-term infants.[2] However, the clinical characteristics, diagnostic criteria and treatment strategies of term neonatal RDS are very different from that in premature infants.

The causes for full-term neonatal RDS are as follows (1) congenital pneumonia from perinatally acquired infections which is the most common cause of term neonatal RDS, (2) transient tachypnea of newborn in infants born through elective caesarean section, (3) Severe birth asphyxia and meconium aspiration syndrome

(MAS),(4) Pulmonary haemorrhage, (5) Inherited disorders of surfactant metabolism.[4] Several criteria for the diagnosis of RDS in full-term neonates have been suggested. From the clinical experiences, together with the diagnostic criteria for premature infants and adults, Liu J et al.[5] suggested the following criteria for diagnosis of full-term neonatal RDS (1) Acute onset; (2) Had an acute explicit perinatal triggering insult: such as severe perinatally acquired infection, elective cesarean section, severe birth asphyxia, meconium aspiration syndrome, etc.(3) Representative clinical manifestations including progressive respiratory distress occurring shortly after birth, characteristic grunting respiration, retractions during inspiration, cyanosis, and reduced or absent breathing sounds;(4) Typical chest x-ray findings, which including hypoexpansion and diffuse, fine granular densities (grade I), air bronchograms caused by the atelectatic air sacs (grade II), ground-glass appearance (grade III) or white lungs caused by diffuse bilateral atelectasis (grade IV);(5) Arterial blood gas analysis showing hypoxia, hypercapnia and oxygen tension/fraction of inspired oxygen ratio (PaO2/FiO2) ≤ 26.7 kPa. Treatment strategies include (1) Broad spectrum antibiotics in case of perinatal acquired infection (2) Mechanical ventilatory support (3) Supplement of exogenous surfactant (4) i- NO therapy in case of PPHN (5) Extracorporeal membrane oxygenation and pulmonary transplantation in case of inherited surfactant disorders.

In a word, RDS is a common severe disease in full-term neonates, it is important to understand its clinical characteristics, diagnostic criteria and treatment strategies for improving the prognosis of these babies. This study aims at studying the maternal and perinatal risk factors for RDS in term neonates by a retrospective case-control study, and thus provide a useful reference for its diagnosis and treatment.

METHODS

This study was conducted in neonatal intensive care unit of tertiary care centre, KIMS hospital and research centre , Bangalore, Karnataka between December 2016 to July 2018. A total of 100 term neonates with RDS were taken as cases and 150 term neonates without RDS were taken as control. Data were collected from the hospital NICU records, maternal and perinatal history was collected from hospital records .

The data collected include mode of delivery, birth asphyxia, premature rupture of membranes (PROM), maternal age at pregnancy, pregnancy hypertension disease, gestational glucose intolerance or diabetes, sex, birth weight, a cord around the neck with compression, oligohydramnios, meconium staining of amniotic fluid, severe fetal distress, and placental abruption. Diagnosis of RDS in these neonates was done using the above said criteria by Liu J et al, the other diagnostic criteria used in this study were as following: severe birth asphyxia was diagnosed as 1.[5] Prolonged (1 hour) antenatal acidosis.[2] Fetal HR - 60 beats/minute.[3] Apgar score -3 at 10 minutes.[4] Need for positive pressure ventilation for 1 minute or first cry delayed 5 minutes. [5] Seizures within 12 to 24 hours of birth.[6] Burst suppression or suppressed background pattern on EEG or amplitude integrated EEG (a EEG) Apgar Score ≤7 at 1 to 5 minutes after birth with umbilical arterial pH <7.15, and with at least one hypoxic-ischemic organ injury (such as hypoxic-ischemic encephalopathy, etc.).[6] Meconium stained amniotic fluid means dark green and foul-smelling amniotic fluid contaminated with meconium. Maternal-fetal infection means fetal-neonatal infectious diseases such as pneumonia/septicemia caused by intra-amniotic infection. Severe fetal distress was diagnosed as a significant abnormality in the fetal heart rate according to the results of fetal heart rate monitoring.[7]

Statistical analysis

Data analysis was conducted using SPSS 16.0 software. A $p<0.05$ was considered to be statistically significant. The $\chi 2$ tests or Fisher's exact text were used for one-way risk factor analysis. Logistic regression analysis was employed to find the correlation of positivity with clinical variables (Adj OR=1, no relationship, Adj OR>1, positive association and Adj OR <1: Negative association).

RESULTS

From the above study it was found that RDS in term neonates is associated significantly with following risk factors like selective cesarean section (x2=7.017, p=0.008), male sex (x2=9.978, p=0.001), small for gestational age (x2=5.889, p=0.015), oligohydramnios (x2=6.667, p=0.009), meconium staining of amniotic fluid (x2=28.65, p=0.001), severe fetal distress (x2=5.979, p=0.014), birth asphyxia (x2=23.27, p=<0.001) , PROM (x2=8.696, p=0.003), and maternal-fetal infection (x2=30.90, p<0.001) (Table 1).

Figure 1 depicts comparison of occurrence of RDS with risk factors, which showed significant association with RDS among risk factors like PIH, PROM,MSAF, Oligohydramnios, Fetal Distress, Severe Birth Asphyxia, Maternofetal Infection. Maternal age at time of pregnancy, cord around the neck with compression, abnormal GTT and placental abruption were not significant risk factors for RDS in term neonates.

The effects of multiple factors on term neonatal RDS were analyzed using logistic regression analysis which showed that severe birth asphyxia (OR: 43.26 ; 95% CI: 3.98-470.39), maternal-fetal infection (OR: 12.24; 95% CI: 2.70-55.47), PROM (OR: 2.641; 95% CI: 1.72-4.05), meconium stained amniotic fluid (OR: 9.71; 95% CI: 4.27-22.07) were the main risk factors showing positive association with RDS in full-term neonates (Table 2).

Table 1: Analysis of risk factors in two groups(n%).

Factors	Cases (total -100) n (%)	Control(total- 150) n (%)	Chi Square Test	p value
Maternal Age				
≥ 35 years	9 (9)	11 (7.3)	0.226	0.634
< 35 years	91 (91)	139 (92.7)		
Mode of delivery				
LSCS	35 (35)	30 (20)	7.017	0.008*
Normal /Assisted Vaginal	65 (65)	120 (80)		
Sex				
Male	75 (75)	83 (55.3)	9.978	0.001*
Female	25 (25)	67 (44.7)		
Birth weight				
SGA	21 (21)	15 (10)	5.889	0.015*
AGA	79 (79)	135 (90)		
Pregnancy induced hypertension				
With	11 (11)	6 (4)	4.639	0.031*
Without	89 (89)	144 (96)		
Abnormal GTT/GDM				
With	8 (8)	8 (5.3)	0.712	0.398
Without	92 (92)	142 (94.7)		
PROM(> 18 hrs)				
With	31 (31)	23 (15.3)	8.696	0.003*
Without	69 (69)	127 (84.7)		
Cord around neck with compression				
With	7 (7)	5 (3.3)	1.765	0.183
Without	93 (93)	145 (96.7)		
Meconium stained amniotic fluid				
With	35 (35)	12 (8)	28.65	<0.001*
Without	65 (65)	138 (92)		
Oligohydramnios				
With	16 (16)	9 (6)	6.667	0.009*
Without	84 (84)	141 (94)		
Abruption placenta				
With	4 (4)	2 (1.3)	1.821	0.177
Without	96 (96)	148 (98.7)		
Severe fetal distress				
With	22 (22)	16 (10.6)	5.979	0.014*
Without	78 (78)	134 (89.4)		
Severe birth asphyxia				
With	20 (20)	3 (2)	23.27	<0.001*
Without	80 (80)	147 (98)		
Materno-fetal infection				
With	34 (34)	10 (6.6)	30.90	<0.001*
Without	66 (66)	140 (93.4)		

LSCS- lower segment caesarean section, GTT- glucose tolerance test, GDM- gestational diabetes mellitus, SGA- small for gestational age, AGA- appropriate for gestational age, PROM- premature rupture of membranes. *Significant P <0.05

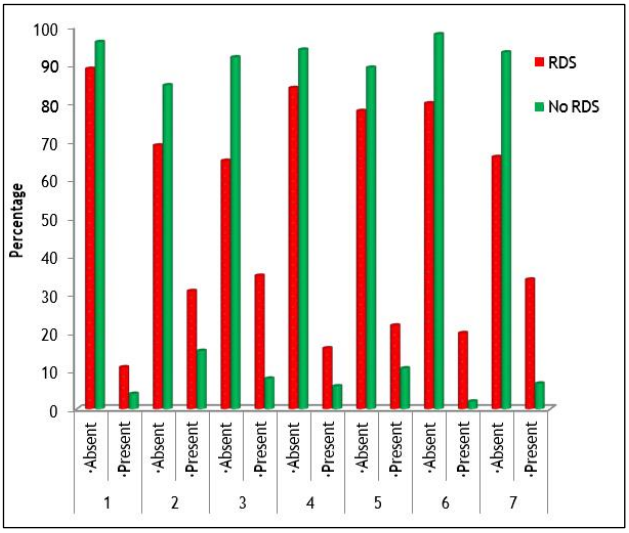
DISCUSSION

The results of this study show that factors like selective cesarean section, male sex, small for gestational age, oligohydramnios, meconium staining of amniotic fluid, severe fetal distress, birth asphyxia, PROM ,and maternal-fetal infection are significantly associated with RDS in full-term neonates. It is well-known that the factors small for gestational age, low birth weight, and

gestational glucose intolerance or diabetes play a role in the mechanisms of RDS. Hence this study focussed on the other factors. The results of our study were similar to study done by Jing Liu et al, where selective cesarean section, severe birth asphyxia, PROM, male sex, and gestational glucose intolerance or diabetes were the main risk factors of RDS in full-term neonates.[8] The mechanism of RDS in selective caesarean section is as there is less activity of amiloride-sensitive sodium channels in alveolar epithelial cells following cesarean section, leading to reduced fluid clearance.[3]

Table 2: Multivariate logistic regression analysis to assess the risk factors of RDS.

Variables	Logistic regression results to predict the RDS				95%CI		
	Logit co- efficient	SE	Wald	P value	Adj OR	Lower	Upper
PIH	-0.44	0.92	0.22	0.637	0.65	0.11	3.95
PROM	2.17	0.27	20.13	<0.001**	2.64	1.72	4.05
MSAF	2.27	0.42	29.44	<0.001**	9.71	4.27	22.07
Oligohydramnios	-0.91	0.99	0.85	0.358	0.40	0.06	2.79
Fetal Distress	-1.91	0.87	4.80	0.028*	0.15	0.03	0.82
Severe Birth Asphyxia	3.77	1.22	9.57	0.002**	43.26	3.98	470.39
Materno Fetal Infection	2.50	0.77	10.55	0.001**	12.24	2.70	55.47



1. PIH, 2. PROM, 3. MSAF, 4. Oligohydramnios, 5. Fetal distress, 6. Severe birth asphyxia, 7. Maternofetal Infection

Figure 1: Comparing occurrence of RDS with risk factors.

Severe birth asphyxia and maternal-fetal infection are the important causes of term neonatal RDS.[5] This may be because of the following two reasons: 1- acute lung injury caused by severe birth asphyxia or maternal-fetal infection decreases the synthesis and secretion of pulmonary surfactant; and 2- hypoxia or maternal-fetal infection inhibits the activity of PS and even leads to its inactivation.

In our study male sex was found to be a significant risk factor for term neonatal RDS. It is explained by Nielsen HC et al, that the female fetal lung produces surfactant earlier in gestation than the male fetal lung.[9] Mechanism being 1- Androgens delay lung fibroblast secretion of fibroblast-pneumocyte factor, which can delay the development of alveolar type II cells and reduce the release of PS. 2- Androgens slow fetal lung development by adjusting the signaling pathways of epidermal growth factor and transforming growth factor-beta. 3- Estrogen promotes the synthesis of PS, including phospholipids, lecithin, and surfactant proteins A and B. 4- Estrogen also improves fetal lung development by increasing the number of alveolar type II cells and by increasing the formation of lamellated bodies.

In our study PROM also showed a positive association with term RDS the mechanism of which was explained by Yang LC et al , in which (1) PROM leads to maternal-fetal infection; Intrauterine infection and chorioamnionitis caused by PROM can result in direct in-jury to the fetal lungs and alveolar type II cells, decreasing the synthesis or release of surfactant. [10] (2) Fetal-neonatal lung inflammation increases the permeability of the alveolar- capillary membrane to both fluid and solutes. This results in plasma proteins entering the alveolar hypophase, which further inhibits the function of surfactant. In our study the risk factors like mothers having PIH, oligohydramnios and severe fetal distress which were significantly associated with RDS did not show positive association in logistic multivariate analysis.

CONCLUSION

In our study risk factors like severe birth asphyxia, maternal-fetal infection, PROM, meconium stained amniotic fluid were showing positive association with RDS in full-term neonates. Hence This study represents a recent reference for the evaluation of maternal and perinatal risk factors for the development of respiratory distress syndrome in term neonates.

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