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Original article

Clinical characteristics, diagnosis, and management outcome of surfactant deficiency respiratory distress syndrome in term and near-term neonates. A retrospective observational study

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Abstract. *Aim:* This study aims to describe the clinical characteristics of SRDS in term and late preterm neonates. *Methods:* This is an observation retrospective chart review of full-term and late preterm neonates born older than 35 to 41 weeks gestation age diagnosed with SRDS. The diagnosis was based on clinical & radiological manifestations of SRDS. *Results:* 1547 neonates were admitted during this period to NICU with a diagnosis of increased work of breathing for further management. 117 cases of term and near-term neonates (mean GA = 36.8 wks) had a confirmed diagnosis of Surfactant deficiency SRDS. Who compared 60 preterm neonates with SRDS less than 35 weeks gestation (mean GA 27.5 wks) as a control. The mean birth weight was 2.8 kg vs 1.1 kg in the preterm group. SRDS occurs more among the male gender (58%), with CS in 78.6% of all diagnosed cases. No apparent cause was found in 28.2%, while 37.6% of all cases were born to mothers with diabetes mellitus, and 27% were born to mothers with either GBs infection, maternal chorioamnionitis, or prolonged rupture of the membrane. *Conclusion:* SRDS is not uncommon among full-term and near-term neonates (10/1000 live birth). By far, the most common associated risk factors are maternal diabetes mellitus and cesarean section. It affects males more than females. Most cases will run a mild-to-moderate course that responds to non-invasive ventilation. (www.actabiomedica.it)

Key words: term newborn, respiratory distress syndrome, surfactant, RDS,

Introduction

Increased work of breathing up to respiratory distress is a common scenario in the delivery room among full-term neonates. Most cases will resolve spontaneously within hours, and even admission to the NICU is not necessary. Transient tachypnea in the newborn is the commonest cause of mild RDS (1). However, it is not uncommon that respiratory distress needs more than just clinical observation. Since the original description of deficiency of the pulmonary surfactant in premature neonates by Avery in 1959, SRDS has most commonly been attributed to the developmental immaturity of surfactant production (2). But in clinical practice, it has been found that SRDS can occur in term and late-term neonates. Many of them were recognized as transient tachypnea at the beginning until clinical behavior started to change, and the typical radiological signs were demonstrated (3).

SRDS in term neonates can be divided into three types (4), The first type is seen with acute respiratory distress which follows a catastrophic pulmonary or non-pulmonary event, such as a hypoxic-ischemic event, meconium aspiration, shock, sepsis, disseminated intravascular coagulation and pulmonary hypertension. All can result in direct injury to the

pneumocyte type □ cells with decreased synthesis, release, or processing of surfactant, in addition, there is increased permeability of the alveolar-capillary membrane to both fluid and solutes. This results in edema of the alveoli and interstitial space, which reduces compliance and functional residual capacity while increasing the physiological dead space (5).

The second type is Idiopathic respiratory distress syndrome (SRDS): Mostly seen in babies born after elective Caesarean sections, the earlier the Caesarean section, the higher the incidence of SRDS in full-term neonates (6-8). The third type of SRDS in term babies is related to inherited surfactant metabolism disorders, which are rare conditions and are associated with significant morbidity and mortality (9,10). In this observational study, the aim was to describe the natural history of the classic SRDS.

Methods

This is a retrospective observational study that examined all inborn singleton ≥ 35 weeks gestational age born at our tertiary level NICU during the period from August 2019 to December 2020 under the diagnoses of respiratory distress and who required any type of respiratory support and oxygen therapy through a nasal cannula, CPAP, NIPPV, or mechanical ventilation. Diagnosis and severity of SRDS were made based on our NICU guidelines adopted with modification and combination of clinical criteria, Radiological findings, and blood gas results (Table 1) (11-14).

We excluded congenital heart and lung diseases, major congenital malformations, confirmed early neonatal septicemia, and primary major genetic conditions like trisomy syndromes. The study also excluded cases diagnosed with clear manifestations of meconium aspiration syndrome, hypoxic-ischemic birth injury, frank congenital pneumonia, and those neonates who required significant resuscitation and intubation in the delivery room.

Data were extracted from the medical record (Cerner™) and respiratory therapy record in our NICU. The data was manually uploaded to the Data Microsoft excel sheet designed based on the study variable. The data sheet included the demographic data, mode of delivery, maternal risk factors, clinical course, and the diagnosis after evaluation of the laboratory and chest- x-ray findings, complications, and treatment given.

Normal distribution of the data was studied with Kolmogorov- Smirnov or Shapiro-Wilk according to the number of observations. Data were expressed as mean. A T-test was used for independent group comparisons. Friedman test was used for the temporal change, followed by the Conover method for the

Table 1. Severity of respiratory distress syndrome used in the study.*

	Mild	**Moderate**	**Severe**
Clinical	Tachypnea > 60/minute, grunting by auscultation, mild subcostal recession, diminished air entry, FIO2 30-40 % for more than 12 hours to keep oxygen saturation more than 90% on CPAP 5-7 mmH2O	Tachypnea > 60, audible grunting, more subcostal recession, and other accessory muscles, poor air entry, FiO2 >40% to keep SO2 above 90% On CPAP 5-7 mmH2O	Tachypnea > 60, audible grunting, more subcostal recession, and other accessory muscles, or apneic attacks, FIO2 ≥40% - 100% on CPAP > 7 mmH2O with frequent desaturation, Cyanosis, apneic spills and/or need intubation for surfactant administration
Radiological	Fine ground glass appearance with clear cardiac borders and air bronchogram within the cardiac shadow.	Fine ground glass appearance with obscured cardiac borders, air-bronchogram beyond cardiac shadow up to the periphery, and small lung volume	Fine or coarse ground glass appearance homogenously distributed all over the lung field with obliteration of cardiac borders and air bronchogram up to the periphery of the lung or white out lung field and/or Pneumothorax
Blood gases	Normal	Increased PCO2 > 45 mmHg	Increased PCO2 > 45 mmHg and Metabolic acidosis pH<7.3

*11-14

paired comparisons. Pearson chi-square for P value. The significant level was set at 0.05 in all tests. All analyses were performed utilizing SPSS for Windows (Statistical Package for Social Sciences) version 17.0 (SPSS Inc., Chicago, IL, USA). The study was approved by the Hamad Medical Research Center with a waiver of consent. (ID MRC-01-21-690 IRB approval: 425403- ABHATH - MRC (HMC)

Result

The study screened; 12000 full-term neonates delivered over 16 months. 1547 neonates were admitted during this period to NICU with a diagnosis of increased work of breathing for further management. 117 cases of term and near-term neonates had a confirmed diagnosis of surfactant deficiency, SRDS. 60 preterm neonates less than 35 weeks gestation who developed SRDS were recruited to compare with. The mean gestation age was 36.8 weeks ±1.65, and the mean birth weight was 2.8 kg± 0.58. SRDS occurs more among the male gender (58%), with Caesarean sections in 78.6% of all diagnosed cases. No apparent cause was found in 28.2%, while 37.6% of all cases were born to mothers with diabetes mellitus, and 27% were born to mothers with either GBS infection, maternal chorioamnionitis, or prolonged rupture of the membrane more than 24 hours. No cases were diagnosed with positive blood cultures. (Table 2) Non-invasive ventilation was the only treatment required in 69% of cases. 26.5% of all cases required surfactant installation. The severity of the clinical course was as follows, mild in 40% of cases moderate in 53.2%, and severe in 6.8% of cases (Fig. 1). Small lung volume was the least frequent radiological feature of SRDS chest x-ray (14%) versus (40%) in the preterm group (P-value < 0.001). (Table 3) Pneumothorax occurred in 16/117 (14.5%) of cases versus 11% in the preterm newborns (P-value =0.6), 7/16 cases were treated conservatively on CPAP. 9/16 of pneumothorax required insertion of chest tube, intubation, surfactant, and mechanical ventilation. No recorded cases of pulmonary hypertension by echocardiography. When surfactant therapy was indicated (26.4% of all cases), a single dose was required in 90% of cases (Table 3).

Table 2. Demographic characteristics.

Variables	Case n=117 (%)	Control n=60 (%)	P-Value
Gender			0.123
Male	68 (58.1%)	42 (70 %)	
Female	49 (41.9%)	18 (30 %)	
Gestation age (mean)	36.8 weeks ±1.65	27.5 weeks± 1.5	<0.0001
Weight (mean)	2.8 ± 0.58	1.1± 0.38	<0.0001
Delivery			0.635*
VD	25 (21.4%)	11 (18.3%)	
C/S	92 (78.6%)	49 (81.7%)	
Apgar score in the first minute	7.8 ±1.8	6.5 ± 1.7	0.001
Apgar score in the Fifth minute	9.0 ± 0.9	8.4 ± 1.0	0.001
Meconium stained liquor	9 (7.7%)	2 (3.3%)	0.256
Maternal GBS	14 (11.9%)	2 (6.7%)	0.151
Maternal Fever/ Chorioamnionitis	6(5.1%)	3 (5 %)	0.97
Maternal DM	44 (37.6%)	20 (33.3%)	0.575
PROM	11 (9.4%)	12 (20%)	0.047

*95 % CI: 0.38 to 1.8 and OR= 0.89

Table 3. Respiratory characteristics.

Variables	Case n=117(%)	Control n=60 (%)	P-Value
SRDS. Grade			0.0014
Mild	47 (40.2%)	17 (28.3%)	
Moderate	62 (53%)	28 (46.7%)	
Sever	8 (6.8%)	15 (25%)	
Chest X-ray finding			
Ground glass	110 (94%)	49 (81.7%)	0.010
Air bronchogram	81 (69.2%)	54 (90%)	0.002
Low lung volume	17 (14.7%)	40 (66.7%)	<0.0001
Surfactant	31 (26.5%)	53 (88.3)	<0.0001
Surfactant Doses			0.101
1 dose	28 (90.3%)	42 (79.2%)	
2 doses	2 (6.5%)	11(20.8%)	
3 doses	1 (3.2%)	0	
Respiratory Support			<0.0001
Non-invasive	81 (69.2%)	7 (11.7%)	
Invasive	36 (30.8%)	53 (88.3%)	
Days on Oxygen	3.75± 4	28.1 ±28	<0.0001
Maximum FIO2 requirement	35%.6 ± 13 %	40± (15 %)	0.002
Pneumothorax	17 (14.5%)	7 (11.7%)	0.599
PPHN	0	3 (5%)	0.015
iNO	0	3 (5%)	0.015

Table 4. Multivariate logistic regression.

			95% CI for the Odds ratio	
Variables	**P value**	**Odds ratio**	**Lower**	**Upper**
Gender	0.756	0.745	0.116	4.8
Delivery	**0.025**	**0.025**	**0.001**	**0.63**
Apgar score in 1 minute	0.257	0.625	0.278	1.407
Apgar score in 5 minutes	0.272	2.142	0.551	8.335
Maternal DM	0.276	2.896	0.427	19.613
PROM	0.069	0.093	0.007	1.207
Surfactant	0.779	1.648	0.050	54.331
FIO2 Requirement %	0.914	1.004	0.942	1.07
Respiratory support	0.935	1.164	0.030	44.66
Length of Hospital stay in days	**0.000**	**0.782**	**0.681**	**0.9**
Feeding difficulties	0.852	0.814	0.093	7.12
Days on FIO2	0.603	1.040	0.898	1.204
Ground glass	**0.927**	**0.887**	**0.068**	**11.564**
Air bronchogram	0.046	0.030	0.001	0.933
low lung volume	0.017	0.057	0.005	0.596

Multivariant logistic regression (table 4) showed a reduction in lung volume (P-value < 0.05) was the least frequent radiologic feature in full-term patients.

Discussion

Embryologically, surfactant synthesis in human alveoli is usually established by the end of the Saccular phase which starts at 24 weeks gestation and continues throughout the third trimester, while the surfactant synthesis process is completed during the alveolar phase (15). This embryological fact is not true all the time, and several factors can affect the synthesis of the surfactant during the third trimester. The main function of the surfactant is to reduce alveolar surface tension, promote a compliant elastic alveolar wall and prevent lung collapse during the end of expiration. Lack of surfactant coating the alveolar surface will lead to poor alveolar expansion and reduction in the alveolar basement membrane surface area and ventilation-perfusion mismatch which is translated clinically as increased work of breathing, oxygen requirement, and disturbed blood gases (15).

The classic SRDS diagnosis usually depends on combining three columns of criteria. Clinical, blood gases, and most importantly the radiological criteria. Clinical presentation and standard chest radiographs remain the most common and useful tools. Rarely in full-term newborns who have SRDS, the maximum radiographic findings may not be present until 24 to 48 hours after birth. The characteristic fine reticular granular pattern and air bronchograms may develop as the infant uses existing surfactant stores in advance of inadequate endogenous production. In addition, exogenous surfactant therapy can alter the natural course of the radiographic findings. Moreover, after the surfactant therapy is unevenly distributed throughout the lungs, areas of the aerated lung may alternate with areas of unchanged RDS. In our study, we observed the most consistent radiologic findings were ground-glass/fine reticular granular appearance of different intensities and air bronchogram, while small lung volume was not a constant sign in most of the x-rays (16).

There are several published criteria for the diagnosis of SRDS in full-term neonates that have been suggested. Bouziri et al adopted the following criteria: (1) Gestational age ≥35 weeks(2); severe and immediate respiratory distress requiring mechanical ventilation with PEEP ≥4 cmH2O and FiO2 ≥ 0.5 during at least 6 hours(3); Dependence on oxygen ≥48 hours(4); Diffuse alveolar damage shown by chest radiography(5); PaO2 ≤60 mmHg under FIO2 ≥ 0.5 (17). Faix et al applied the following criteria to neonates: (1) they are full term (2) they had diffuse bilateral alveolar opacification on chest radiographs during the acute illness; (3) each had acute perinatal triggering insult; (4) they required continuous positive pressure ventilation for at least 48 hours with FiOS > 0.50 for at least 12 hours(5); they needed positive end-expiratory pressure of ≥ 6 cm of H2O within 3 days of the triggering event and (6) There were no other known causes for these clinical conditions (18). LIU Jing et al, believe that all these criteria have some limitations, he suggested the application of the same clinical criteria that applied to the preterm newborn, in addition to clear evidence of perinatal events (4) . In his study, acquired infection (pneumonia/septicemia) was the most common cause of full-term neonatal SRDS, and the second common cause was a cesarean section, and It was more common among boys than in girls. The onset of the disease in term neonates was earlier, more severe, and more likely to progress into PPHN (4). Contrary to his findings, newborns in our study ran mild to moderate courses, had no significant pulmonary hypertension, and had shorter mechanical ventilation courses. As well, maternal diabetes mellitus was the leading cause of SRDS followed by idiopathic causes, while a history of proven maternal infection, maternal fever, and or prolonged rupture of the membrane was counted for 26% of recruited cases (Table 2). We excluded frank congenital pneumonia and early neonatal sepsis. In our study, only 31 cases received surfactant (26.5%), however single-dose surfactant therapy was enough among our sample 90% versus 79% in preterm infants (Table 3). A systematic review and meta-analysis by Ramaswamy et al (19) reported that 45% of cases received surfactant. This variation is likely due to the inclusion of 34 weeks of gestation in his stud sample cases. Infants who have SRDS may do well with continuous positive airway pressure or may require ventilation. Surfactant often improves pulmonary mechanics significantly but has little effect on the overall outcome, which is favorable in most cases (20). The

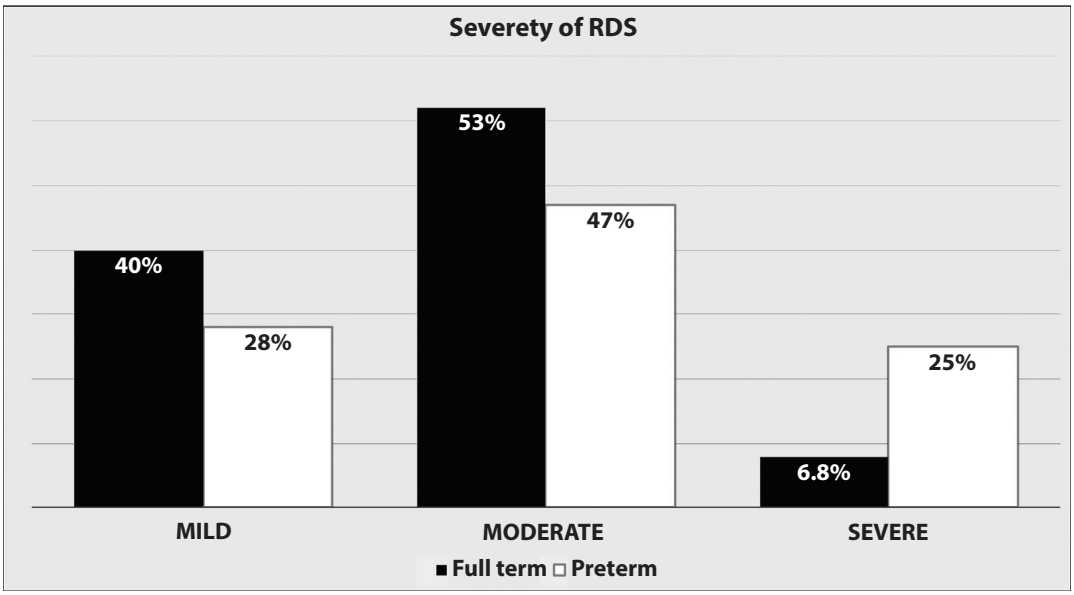

Figure 1. Severity of the clinical presentation.

mortality rate was zero in our study which indicates early intervention in all cases.

In China in 2012, Huiqing Sun, a large comprehensive observational study reported a very high rate of SRDS where he reported the incidence of SRDS in late preterm infants as high as 13% which was one-third of that in very preterm infants and the incidence in term infants was as high as 15%. He as well reported CS in 49% versus 79% in our study (21). Ramaswamy et al reported a rate of 8-10 per 1000 newborns at this gestation age which is the same in our study. Cesarean sections occurred in 79% of all cases in our study. This is consistent with the literature (19).

Comparing SRDS in full term against preterm is not only intended to demonstrate differences but as well highlight similarities. Although the Multivariate logistic regression analysis in table 4 demonstrated that the main significant difference between full-term and preterm groups was the radiological appearance and mode of delivery, it is worth noticing that maternal diabetes was a major associated risk factor in both groups.

Conclusion

In this study, our main goal is to describe the clinical behavior and characteristics of SRDS in full-term and near-term newborns delivered in modern tertiary NICUs. Maternal diabetes mellitus is the main risk factor associated with SRDS in both full-term and preterm followed by Caesarean section. While no clear cause was found in 28.2% of cases. Most cases ran a milder course, but the risk of pneumothorax is significant. In modern NICUs, the mortality rate should be minimal when diagnosis and early intervention are applied. Physicians dealing with newborn infants should acknowledge the fact that idiopathic SRDS does exist in full-term and late preterm infants and its rate is 10/1000 of births and these babies usually are delivered in level one and two perinatal centers. Physicians are requested to have a high index of suspicion of such disease and to establish the right treatment early in the course of the disease and prompt timely management should leave minimal morbidity and mortality.

Abbreviations: CMV: Conventional mechanical ventilation; CPAP: Continuous positive airway pressure; CS: Caesarean section; FIO2: Fraction of inspiration oxygen; INSURE: Intubation-surfactant-extubation; NIV: Non-invasive ventilation; NICU: Neonatal intensive care unit; PS: Pulmonary surfactant; SRDS: surfactant deficiency Respiratory distress syndrome.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity

interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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