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Original Article

Analysis of neonatal respiratory distress syndrome among different gestational segments

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Abstract: Objective: To find more effective diagnosis and treatment of NRDS through comparatively analyzing the different gestational neonates with respiratory distress syndrome in risk factors, clinical characteristics, treatment and prognosis. Methods: The clinical data of 232 neonates were retrospectively analyzed who had been admitted into the neonatal intensive care unit and diagnosed with NRDS from January 2008 to December 2010. These cases were divided into three groups according to gestational age, which included full-term group, late preterm and early preterm group. Statistical analysis was used to detect the differences of relative factors among the three groups. Results: For pathogen, the full-term and late preterm infants accounted for more than 50% The majority of full-term infants were less than 39 weeks, taking up 83.7%. As many as 61.1% of the late preterm infants were born at maternal age over 30 years. The incidence of Cesarean section was high among the three groups, especially the full-term (90.7%) and late preterm group (86.1%). For clinical features, full-term infants had late onsets more than 12 h after birth. Air bronchogram could be found commonly in early preterm neonates, influencing 92% of them. However, it was rare in the other two groups. The incidence of lung infection in each group was all about 50%. In addition, Gas leakage and PPHN were more common complications in full-term and late preterm group, while for the early preterm group was the bronchopulmonary dysplasia and intracranial hemorrhage. For treatment, the proportions of full-term infants receiving application of HFOV and NO were 57.0% and 24.4%, and for late preterm infants were 36.1% and 22.2%. The application of HFOV and NO was not as much to early preterm infants as other groups. There was no significant difference in the duration of invasive ventilation between all groups. However, the noninvasive ventilation time after extubation was as long as 10.1±0.5 days in early preterm infants. The proportions of infants receiving application of PS were 53.5%, 83.3% and 81.8%, respectively. OI values improved greatly 2 h after application of PS on early preterm infants. However, the obvious difference was found only after 24 h for full-term and late preterm infants.Conclusion: Besides early preterm infants, full-term and late preterm have the growing trend in the pathogenesis of NRDS. Infants of different gestational age have their own characteristics of the risk factors, which cesarean section impacts greatly on the incidence of term and late preterm infants. The clinical feature, chest X-ray changes and common complications were characteristics between term and premature infants with NRDS. The PS treatment work slower in term and late preterm infants, who needed more HFOV and NO treatment.

Keywords: Respiratory distress syndrome, neonate, gestational age

Introduction

Neonatal respiratory distress syndrome (NRDS) is a severe respiratory disease in infants, which frequently happened in premature infants [1]. It is the most common cause for admission to the Neonatal Intensive Care Unit (NICU), with the clinical symptoms like tachypnea, poor feeding, nasal flaring, grunting, cyanosis, intercostal retraction and reduction of respiratory sounds in pulmonary auscultation. Respiratory distress is seen in 6%-7% of newborns, the highest incidence being among preterm neonates, followed by post-term and term infants [2]. It is recently found that the incidence of NRDS in late preterm infants has an increasing trend, which accounts for nearly a third of children with NRDS [3, 4]. Respiratory distress syndrome is a common cause of respiratory distress in preterm neonates. The surfactant deficiency is the pathophysiological basis of NRDS, which is closely associated with the gestational age [5] or birth weight [6]. Chest radiographic findings and acidosis are the main diagnostic criteria of NRDS [7]. The present study aims to play a guiding role in NRDS diagnosis and treat-

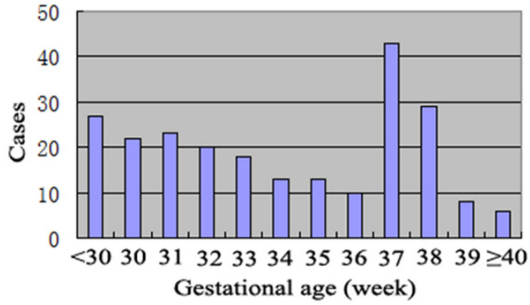

Figure 1. The cases of NRDS at different gestational ages.

ment in clinic by comparing the differences of NRDS risk factors, clinical characteristics and treatment effects at different gestational ages.

Material and methods

Material

The complete medical records of 232 neonates, who were admitted into intensive care units and diagnosed with NRDS from January 2008 to December 2010, showing several clinical features such as serious cardiac abnormalities, severe infection, cardiac pulmonary edema. They were divided into three groups according to gestational age, i.e. full-term group (86 cases, gestational age ≥ 37 weeks), late preterm (36 cases, gestational age from 34 to $36^{6/7}$ weeks) and early preterm group (110 cases, gestational age from 28 to $33^{6/7}$ weeks). The full-term accounted for 37.1% and the average gestational age was 38.6±1.07 weeks, the average body weight was 3.09±0.57 kg. The late preterm accounted for 15.5% and the average gestational age was 35.1±1.6 weeks, the average body weight was 2.19±0.57 kg. The early preterm accounted for 47.4% and the average gestational age was 30.9±1.6 weeks, the average body weight was 1.71±0.48 kg.

Methods

The case data of three groups were retrospectively analyzed and the related factors, clinical characteristics, treatment and effects of neonatal respiratory distress syndrome were compared, i.e. (1) the general condition of onset including maternal factors such as age, pregnancy-induced hypertension (PIH), diabetes mellitus (DM), delivery way, parity; infantile factors such as gestational age, gender, asphyxia, premature rupture of membranes, inhalation syndrome; placental and umbilical factors such as placental abruption, placenta previa, edema, lumps around the neck of umbilical cord; (2) clinical characteristics including onset time, main symptoms, X-ray characteristics; common complications including lung infection, gas leakage, neonatal persistent pulmonary hypertension (PPHN), patent ductusarteriosus (PDA), intracranial hemorrhage (IVH), cardiac insufficiency; (3) treatment and outcome including the mode and duration of invasive mechanical ventilation, NO treatment, oxygenation index (OI) after application of alveolar surface active substance and PS drug (100-200 mg/kg), of which the OI = inhaled oxygen volume fraction (FiO_2) × mean arterial pressure (MAP) × 100/ PaO_2, the administration frequency, the length of staying. Neonatal respiratory distress syndrome and the complications of diagnostic criteria came from the new fourth edition of *Practical Pediatrics* [3]. The questionnaire data obtained was analyzed by the statistical software SPSS 17.0. The count data were for chi-square test and measurement data were for t test and variance analysis.

Results

The gestational age distribution of NRDS infants

The NRDS incidence among different gestational ages in the 232 cases were shown in **Figure 1**. The premature infants were increasing with the gestational age, while the incidence was gradually reducing. Generally NRDS occurred in infants at gestational age < 39 weeks (83.7%). There were only 14 cases at gestational age ≥ 39 weeks.

Comparing the factors of NRDS incidences between different groups

The related factors causing NRDS and factors with statistical differences among the groups were shown in **Table 1**. There was a significant difference in the incidences of various factors between full-term group and early preterm group. Maternal age more than 30 years accounted for more in late preterm group. Among the factors, the incidence of Cesarean section was high in each group, in all 71.1%. The selective Cesarean section of full-term and late preterm groups was more common than that of the early preterm group.

Table 1. Comparison of NRDS risk factors (%)

Risk factors	Full-term group (86 cases)	Late preterm group (36 cases)	Early preterm group (110 cases)	χ^2	P	*P1*	*P2*	*P3*
Maternal age ≥ 30	34 (39.5)	22 (61.1)	36 (32.7)	9.132	0.01	0.029	0.324	0.003
PIH	5 (5.8)	10 (27.8)	19 (17.3)	10.934	0.004	0.002	0.03	0.17
GDM	3 (3.5)	2 (5.6)	1 (0.9)	2.766	0.251	/	/	/
CS	78 (90.7)	31 (86.1)	56 (50.9)	41.864	0.000	0.67	0.00	0.00*
Selective CS	35 (40.7)	19 (52.8)	24 (21.8)	14.716	0.001	/	/	/
Parity ≥ 2	51 (59.3)	17 (47.2)	65 (59.1)	5.116	0.77	/	/	/
Placenta abnormality	9 (10.5)	4 (11.1)	19 (17.3)	2.139	0.343	/	/	/
Umbilical cord abnormality	32 (37.2)	8 (22.2)	13 (11.8)	17.663	0.000	0.11	0.00	0.12
Male infant	60 (69.8)	24 (66.7)	85 (77.3)	2.197	0.333	/	/	/
PROM	6 (7.0)	27 (24.5)	33 (16.8)	10.586	0.005	0.09	0.001	0.53
Inhalation syndrome	12 (14.0)	5 (13.9)	4 (3.6)	7.452	0.024	1	0.02	0.07
Low Apgar score	42 (48.8)	23 (63.9)	84 (76.3)	15.919	0.000	0.13	0.00	0.14
0~3	1 (1.16)	2 (5.56)	15 (13.6)	12.258	0.002	/	/	/
4~7	41 (47.7)	21 (58.3)	69 (62.7)	4.509	0.105	/	/	/

P1: *p*-values between full-term group and late preterm group; P2: *p*-values between full-term group and early preterm group; P3: *p*-values between late preterm group and early preterm group.

Table 2. Comparison of air-filled bronchi between severe NRDS groups (%)

Group	Full-term group (51 cases)	Late preterm infant group (21 cases)	Early preterm infant group (74 cases)
Air-filled bronchi (+)	4 (7.8)	7 (30.4)	68 (92.0)
χ^2		90.157	
p		0.000	

Clinical characteristics

The onset time of NRDS was almost within 6 h after birth. In present study, there were 6 cases (7%) with onset time > 12 h in the full-term group, of which 2 cases were after 24 h. And the full-term infants showed obesity. The preterm infants showed shallow short breath, even apnea. However, the full-term infants showed deep and fast breath. In regard to the pulmonary penetrability of chest X-ray radiography, full-term infants presented with "white lung" change, while early preterm infants showed small pulmonary fields with narrow upper part and wide lower part. Air-filled bronchi were more common in severe NRDS, as shown in **Table 2**.

The incidences of complications in each group were shown in **Table 3**. The incidences of HIE and BPD had significant differences between different gestational ages. Gas leakage and persistent pulmonary hypertension were dominant in full-term and late preterm infant groups. However, the incidence of intracranial hemorrhage was obviously higher in early preterm group.

The NRDS treatment and effect

The comparison of machine model selection, the application and aeration time of NO in each group were shown in **Tables 4** and **5**. The amounts of HFOV and NO application in full-term and late preterm group were more than early preterm group. The CPAP duration time after weaning of early preterm group was longer than the other two groups. The application of the alveolar surface active substances (PS) and effect evaluation were shown in **Tables 6** and **7**. The PS application proportion of full-term group was less than the preterm group, and PS worked slowly in full-term and late preterm group.

The hospitalization of early preterm group (averagely 34.8±1.47 days) was longer than full-term group and late preterm group (averagely 20±1.36 days). There was no significant difference of cure rates (averagely 91%) among

Table 3. Comparison of complications (%)

Complications	Full-term group (86 cases)	Late preterm group (36 cases)	Early preterm group (110 cases)	χ^2	P
Pulmonary infection	36 (41.9)	17 (47.2)	49 (44.5)	0.325	> 0.05
Gas leakage*	13 (15.1)	2 (5.6)	1 (0.9)	16.551	< 0.05
PPHN*	10 (11.6)	4 (11.1)	1 (0.9)	12.837	< 0.05
BPD*	0	0	10 (9)	14.467	< 0.05
PDA	31 (36.0%)	12 (33.3%)	55 (50.0%)	5.238	> 0.05
Cardiac insufficiency	6 (7.0%)	5 (13.9%)	9 (8.2%)	1.59	> 0.05
HIE*	16 (18.6)	1 (2.8)	0	29.808	< 0.05
Intracranial hemorrhage*	4 (4.7%)	1 (2.8%)	17 (15.5%)	8.795	< 0.05

*P < 0.05.

Table 4. Comparison of breathing machine model choice and NO application (%)

	Full-term group (86 cases)	Late preterm group (36 cases)	Early preterm group (110 cases)	χ^2	*P*
CPAP	3 (3.5)	2 (5.6)	13 (11.8)	5.195	> 0.05
SIMV*	34 (39.5)	21 (58.3)	76 (69.1)	17.212	< 0.05
SIMV+HFOV*	49 (57.0)	13 (36.1)	21 (19.1)	30.153	< 0.01
NO application*	21 (24.4)	8 (22.2)	5 (4.5)	17.191	< 0.01

*P < 0.05.

the three groups and the mortality rate after treatment ceasing was 9%.

Discussion

In present study, the late preterm and full-term accounted for 52.6%, where the majority of full-term infants were less than 39 weeks (83.7%). The incidence of Cesarean section was the highest among the three groups, especially the full-term and late preterm group (89.3%). The late preterm group had a relatively old-aged mothers. The reasons are the following: (1) the influence of social factors (good economy conditions, one-child policy, proper nutrition during pregnancy and mistaken belief in Cesarean section) and the increasing trend for elderly parturients to choose the Cesarean section; (2) the influence of Cesarean section in NRDS: lung fluid retention to damage neonatal lung inflation and to inhibit PS secretion of alveolar type II cells; insufficient activation of sympathetic nervous system from Cesarean section leads to catecholamine and glucocorticoid secretion, resulting in decreased lung maturity [8]; head congestion after transient hypoxia caused reflex excitation of respiratory center to induce asphyxia after birth, inhibiting PS secretion by alveolar type II cells to cause NRDS [9-11]. Therefore, unless there is clear evidence to prove fetal lung maturity, it is not generally recommended that selective Cesarean section be adopted in parturients at gestational age < 39 weeks. For late preterm infants with high risk factors, it is advisable to use selective Cesarean section and to promote lung maturity [9, 12]. (3) Because the early symptoms of full-term NRDS were not typical or just wet lung, which cannot get enough attention or appropriate treatment to prevent it from developing.

Other influential factors were also impacting differently at different gestational ages. Likewise the incidence of inhalation syndrome and abnormal umbilical cord were higher in full-term and late preterm group. The gestational hypertension and premature rupture of membranes had a higher incidence in early preterm group. This is mainly because of intrauterine distress, amniotic fluid dung and umbilical cord abnormality occurring in the full-term or late preterm as the indication of Caesarean section. As the pregnancy-induced hypertension and premature rupture of membranes were the common reasons for prematurity, the incidence of NRDS was high. Late preterm was between early preterm and full-term, which could be impacted by both factors.

In this study, the incidence of low Apgar score in early preterm group was 76.3%, higher than full-term (48.8%). Those who got only 0-3 points accounted for 13.6% which did not completely explain that the preterm group had more serious asphyxia than full-term. Because of PS deficiency, respiratory distress after birth, low muscle tone, poor response to stimuli due to respiratory center dysplasia, the Apgar scores of the premature were often lower than the mature.

Table 5. Comparison of respiratory support time ($\bar{x} \pm s$)

	Full-term group (86 cases)	Late preterm group (36 cases)	Early preterm group (110 cases)	t	*P*
Breathing machine time (D)	8.0±0.6	6.4±0.8	6.9±0.5	1.321	> 0.05
CPAP duration time after weaning (D)*	4.3±0.6	6.7±0.9	10.1±0.5	4.743	< 0.05

*P < 0.05.

Table 6. Comparison of PS application (%)

	Full-term group (86 cases)	Late preterm group (36 cases)	Early preterm group (110 cases)	χ^2	*P*
PS application*	46 (53.5)	30 (83.3)	90 (81.8)	21.936	< 0.05
Repeated administration	5 (5.8)	1 (2.8)	7 (6.4)	0.784	> 0.05

*P < 0.05.

Table 7. Comparison of OI value after treatment ($\bar{x} \pm s$)

	Full-term (83 cases)			Late preterm (34 cases)			Early preterm (97 cases)		
	Cases	2 h after treatment	24 h after treatment	Cases	2 h after treatment	24 h after treatment	Cases	2 h after treatment	24 h after treatment
PS application	46	22.3±4.3	17.9±2.8	30	19.4±3.8	16.7±2.9	82	18.6±3.4	14.7±3.9
No PS application	37	23.0±3.5	20.3±3.5	4	20.6±3.1	18.6±3.3	15	21.6±2.9	17.9±3.1
t		0.27	4.82		1.32	7.83		3.57	4.25
P		> 0.05	< 0.05		> 0.05	< 0.05		< 0.05	< 0.05

Therefore, application of Apgar score to evaluate premature infants should involve its own factors and combine the blood gas analysis and clinical manifestations.

The onset time of NRDS was almost 2-6 h after birth. In present study, there were 6 cases (7%) in full-term group with onset time > 12 h. And 2 cases were > 24 h. The possible explanations are the following: Pulmonary immaturity and lack of PS in premature infants induced early onset of NRDS. The alveolar PS synthesis of the full-term was relatively normal and more affected by Cesarean section or other factors, and/or pulmonary fluid retention inhibited PS activity. The full-term infants showed symptoms of distress, mainly gas leakage, indicating that the speed of the liquid should be controlled throughout treatment. The premature infants had shallow short breath, even apnea. However, it was deep fast breath as for the full-term, which largely resulted from respiratory center dysplasia and vulnerable inhibition coming from hypoxia in premature infants. The full-term had a strong hypoxia compensatory ability as a consequence of relatively mature respiratory center and lungs.

The chest X-ray radiography of NRDS proved different at these gestational ages. In addition to reduction of light transmittance, early premature group showed small pulmonary fields with narrow upper part and wide lower part, and air-filled bronchi in serious cases. Full-term group showed no obvious lung volume change, but white-lung change in serious cases. This was mainly associated with NRDS caused by lack of primary PS, alveolar atrophy, more obvious atelectasis. However, the full-term was characterized by light transmittance reduction in chest radiograph.

In clinical complications, the average incidence of pulmonary infection was 44%. PDA was 42.2%, which has no obvious difference among the three groups. co-infection was more likely to occur because of critical condition in NRDS, mechanical ventilation treatment and neonatal autoimmunity. The full-term and late premature group showed PPHN and gas leakage. However, early premature group suffered bronchial pulmonary dysplasia (BPD) [13]. Because the full-term and late premature infants had a good development of pulmonary arteriole middle smooth muscle. On suffering hypoxia and aci-

dosis, the small arteries were in spasm, thus pulmonary artery resistance was increasing and caused PPHN [14, 15]. Persistent pulmonary hypertension will be lateral or in both sides, which is more common in terms of PDA in full-term. But its clinical symptom is not obvious in regard to refractory hypoxemia or differences in purple. The occurrence of PDA was related to immaturity, and under the influence of hemodynamics, the clinical symptom is obvious.

In this study, the incidence of gas leakage in full-term group was higher than the late preterm group, and lower in early preterm group. The possible mechanisms were the following: When NRDS occurred in full-term and late preterm infants, PS distribution was asymmetrical, and the alveolar radius was different. The smallest alveolar radius was the first atrophy and showing progressive atelectasis, lung compliance reduction, alveolar ventilation distribution asymmetryin combination with their own compensatory ability, causing a gas leakage by excessive expansion of alveoli. Therefore, it should be advisable to keep low parameters, lung protection strategy and reduce the occurrence of gas leakage in the treatment.

In complications with central nervous system injury, the full-term group showed HIE and the incidence was 18.6%. The preterm group presented with intracranial hemorrhage and incidence was 15.5%, mainly consisting of the subependymal hemorrhage and intraventricular hemorrhage. The main difference of brain injury between the gestational ages was closely related to its anatomical physiology features and the choice of hypoxia vulnerability.

In the aspect of treatment, the mechanical ventilation mode between the three groups were predominantly SIMV, while high frequency oscillatory ventilation and NO inhalation were performed more in full-term and late premature groups. Because co-PPHN was common in the full-term and late preterm infants, application of high frequency ventilation and NO can better improve oxygenation and reduce pulmonary pressure. Through the comparison of duration of mechanical ventilation, the duration time of each group was 7-8 days. After using the withdraw machine, the noninvasive ventilation time was increased with the gestational age decreased between the three groups. This was mainly because of the immaturity of organs and systems at low gestational ages.

In this study, the proportion of application of PS in full-term (53.5%) was significantly lower than the late preterm infants (83.3%) and early preterm infants group (81.8%), which resulted from relatively large body weight of full-term infants, more PS demand, and economic ability. Based on PS oxygenation index (OI) change after treatment, it was found that the PS worked slowly, blood gas analysis and oxygenation index improvement were not obvious in the short term with reference to the full-term and late preterm infants. The main reasons are the following: Early premature NRDS infants lack primary PS so that the effect is obvious after application of PS. The full-term and late preterm pathological changes mainly stemmed from alveolar capillary permeability increase after hypoxia and serious exudative pulmonary edema to dilute and inhibit PS function. Although PS worked slowly in full-term NRDS, we observed that the application of PS could relieve clinical symptoms to reduce the ventilator parameters and reduce the lung injury. Therefore, PS is still the major measure in the treatment of NRDS at different gestational ages. Enough doses should be guranteed for the treatment of late preterm infants and full-term infants. After administration of mechanical ventilation and PS, the late preterm group had higher incidence than the full-term group. But there were no obvious differences in the treatment time and therapeutic effect, which suggested that it is more difficult to cure late premature NRDS, entailing PS treatment.

For the length of hospitalization, early preterm group had a longer hospital time, which did not suggest that the treatment of NDRS was difficult. It was also related to immaturity of organ development in preterm infants. For the cure rate, there was no difference between the three groups. The reasons are the following: (1) Early preterm group did not include those who had their treatment terminated; (2) PS was in great demand (200 mg/kg) in full-term and late preterm group, who unfortunately failed to receive enough and repeated drug use because of economic reasons.

In conclusion, the incidence of full-term and late preterm infant has increased. Cesarean section should be strictly adopted clinically,

especially for those at gestational age < 39 weeks. For late preterm infants associated with high risk factors, it is advised that treatment should be given for promoting lung maturity before selective Cesarean section and that prevention of NRDS be put on the agenda. Different gestational ages have their own particularities in clinical characteristics. PS application is still the main treatment measure and adequate application is the key to ensuring the effect of treatment. Attention should be paid to model selection and parameter setting when breathing machine is used in order to reduce the occurrence of complications and improve the cure rate and quality of life.

Disclosure of conflict of interest

None.

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