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Original Article

Risk factors for respiratory distress syndrome among Chinese infants of 34-42 weeks gestational age: a multi-center observational study

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Abstract: To compare the risk factors for respiratory distress syndrome (RDS) at different gestational ages among Chinese infants 34-42 weeks of gestational age (GA), we reviewed the clinical records of 4,032 newborns. The case (RDS) and control groups were subdivided into three groups according to GA: 34-36 weeks, 37-38 weeks, and 39-42 weeks. An Apgar score of < 7 at 5 min post-birth, male gender and gestational diabetes were independent risk factors for RDS in late preterm and term infants. For infants of 34-36 weeks GA, additional independent risk factors included placental abnormalities and cesarean section, whereas the administration of antenatal dexamethasone and increased gestational age were protective. For infants of 37-38 weeks GA, additional risk factors included meconium stained amniotic fluid and cesarean section without labor, and increased gestational age was also protective (OR = 0.59). Fetal distress and umbilical cord abnormalities were the additional risk factors for infants of 39-42 weeks gestational age, but not for infants of 37-38 weeks gestational age. The results of the current study showed that an Apgar score of < 7 at 5 min post-birth, male gender and gestational diabetes were independent risk factors for both late preterm and full-term infants with RDS. For newborns of 34-38 weeks gestational age, the incidence of RDS decreased with advancing gestational age, and cesarean section was found to increase this risk, more so in cesarean delivery without labor. The administration of antenatal dexamethasone was found to reduce the incidence of RDS in late preterm infants.

Keywords: Gestational age, risk factor, neonate, respiratory distress syndrome, antenatal dexamethasone

Introduction

Neonatal respiratory distress syndrome (RDS) remains a major cause of morbidity and mortality in premature babies. The production of pulmonary surfactants increases with advancing gestational age, and antenatal glucocorticoid administration can prevent RDS effectively in the event of unavoidable premature delivery (gestational age < 34 weeks). The number of late preterm infants is increasing [1, 2], as is the incidence of RDS, even beyond 34 weeks of GA [3, 4]. Although a deficiency of pulmonary surfactant often underlies the development of RDS in these infants, other factors should be considered when RDS occurs in babies delivered nearer to term or full-term, such as mode of delivery, perinatal hypoxia, and ethnicity [5-7]. Among term/preterm neonates, it is reasonable to expect that the risk factors of RDS at varied gestational ages are also different [8]. In the past, most studies supported the conclusion that premature infants < 34 weeks of GA were at a higher risk for RDS due to a developmental deficiency involving surfactant production. However, the causes of the pathogenesis of neonatal RDS after more than 34 weeks GA remain unknown [9]. Therefore, in this study we retrospectively analyzed data from 4,032 Chinese infants delivered late preterm and term, to provide a basis for the clinical assessment and prevention of neonatal RDS in Chinese infants ≥ 34 weeks of gestation.

Materials and methods

Subjects

To facilitate data collection and statistical analysis, we retrospectively reviewed clinical re-

cords of hospitalized infants of 34 to 42 weeks GA in the first 10 days of each month between January 1, 2014 and December 31, 2015. These infants were admitted to our Neonatal Intensive Care Unit (NICU) and 11 other units across Jilin Province in northeastern China. The collaborating NICUs strictly abided by neonatal RDS diagnostic criteria [4, 10, 11], which were: 1) acute onset; 2) the characteristic clinical manifestations of progressive respiratory distress occurring shortly after birth, tachypnea, retractions, expiratory grunting, nasal flaring, reduced or absent breath sounds, severe dyspnea requiring continuous positive airway pressure support at least 72 hours or instillation pulmonary surfactant; 3) typical chest X-ray findings including diffuse fine granular densities, air bronchograms, blurred cardiac borders or white lung; 4) blood gas analysis showing OI (FiO_2 × MAP/PaO_2) > 10 and/or hypoxemia or hypercapnia. We excluded infants with documented systemic infection, chromosomal anomalies, or congenital cardio-pulmonary anomalies that could contribute to respiratory distress. We did not include infants hospitalized for less than 24 hours.

We collected pertinent clinical data from neonatal and maternal records. Modes of delivery were divided into vaginal, cesarean section (CS) with labor, and cesarean section without labor. Placental abnormalities included placenta previa and abruption. Umbilical cord abnormalities included: nuchal cord, short or thin umbilical cord, and cord discoloration. Prolonged rupture of the membrane was defined as rupture of the membrane more than 18 hours prior to delivery. Antenatal dexamethasone administration was defined as intramuscular injection of dexamethasone 6 mg/dose, every 12 hours, for a total of 4 doses given at least 24 hours prior to delivery.

Grouping

To compare the possible risk factors of RDS at different gestational ages, all participants were divided into the case group and control group based on the presence or absence of RDS diagnosis, and then further categorized into three groups according to GA: 34-36 weeks (*late preterm* infants, $34^{0/7}$-$36^{6/7}$ weeks), 37-38 weeks (*early full-term* infants $37^{0/7}$-$38^{6/7}$ weeks), and 39-42 weeks (*mature full-term* infants, $39^{0/7}$-$42^{0/7}$ weeks).

Statistical analysis

The Chi-square test or Fisher's exact test was used for the one-way risk factor analysis of each gestational age group; Student's *t* test was used for the comparison of birth weight and maternal age between the case and control groups, and the data are expressed as the mean ± SD. Significant factors were analyzed via one-way risk factor analysis and logistic regression analysis for each GA group. $P < 0.05$ was considered statistically significant. The data analysis was conducted using SPSS 19.0 (Inc., Chicago, IL, USA).

Results

Of the 4,075 infants who underwent screening, 4,032 eligible participants were enrolled. We excluded patients with congenital heart disease (n = 16), other major congenital defects (n = 9), and a definitive diagnosis of meconium aspiration syndrome or infection (n = 18). The proportion of infants of Han ethnic background was 98.4%. Of the 4,032 infants enrolled, a total of 381 (9.5%) were diagnosed with RDS. These cases were divided into three GA groups: 34-36 weeks GA (187 cases, 19.9%), 37-38 weeks GA (132, 7.2%), and 39-42 weeks (62 cases, 4.9%). The control group was divided into three groups using the same criteria.

One-way risk factor analysis showed that risk factors for RDS were different in each GA group

There was no significant difference in maternal age or multiple deliveries between the case and control groups, in any of the GA groups. However, other multiple significant differences were noted, and these differed among the three GA groups (**Table 1**). Among late preterm infants, several aspects were statistically different between the RDS cases and the controls (GA 34-36 weeks), including gestational age, male, birth weight, antenatal dexamethasone administration, mode of delivery, gestational diabetes (GDM), premature rupture of membrane (PROM), placental abnormalities, and Apgar < 7 at 5 min post-birth. For both groups of term infants (37-38 weeks and 39-42 weeks), risk factors for RDS included meconium staining of amniotic fluid (MSAF), GDM, Apgar < 7 at 5 min post-birth, and male gender. Like the late preterm groups, gestational age and delivery

Table 1. Factors associated with RDS in three gestational age groups [n%, x ± s]

	34-36 weeks			37-38 weeks			39-42 weeks		
	RDS group (n = 187)	Control group (n = 754)	*P*-value	RDS group (n = 132)	Control group (n = 1699)	*P*-value	RDS group (n = 62)	Control group (n = 1198)	*P*-value
Maternal age	28.0±5.2	281±5.1	0.742	28.5±5.1	28.4±4.6	0.074	27.2±4.4	28.2±4,3	0.565
Birth weight (g)	2398.6±616.9	2500.4±514.9	0.009**	3228.7±604.6	3274.5±972.2	0.352	3367.7±675.6	3371.6±434.3	0.820
Multiple delivery	91 (48.7)	361 (47.9)	0.482	60 (45.5)	813 (47.9)	0.595	28 (45.2)	506 (42.2)	0.650
Apgar < 7 at 5 min	24 (12.8)	48 (6.4)	0.003**	11 (8.3)	61 (3.6)	0.007**	8 (12.9)	57 (4.8)	0.005**
Placental abnormalities	26 (13.9)	63 (8.3)	0.020*	6 (4.5)	36 (2.1)	0.072	2 (3.2)	13 (1.1)	0.130
Umbilical cord abnormalities	12 (6.4)	55 (7.3)	0.676	10 (7.6)	218 (12.8)	0.078	4 (6.5)	197 (16.5)	0.036*
Fetal distress	8 (4.3)	31 (4.1)	0.918	13 (9.8)	100 (5.9)	0.068	14 (22.6)	54 (4.5)	0.000**
Antenatal dexamethasone	14 (7.5)	144 (19.1)	0.000**	5 (3.8)	113 (6.7)	0.197			
PROM	45 (24.1)	130 (17.2)	0.032*	10 (7.6)	146 (8.6)	0.069	4 (6.5)	80 (6.7)	0.944
GDM	21 (11.2)	36 (4.8)	0.001**	19 (14.4)	53 (3.1)	0.000**	6 (9.7)	39 (3.2)	0.008**
PIH	36 (19.3)	111 (14.7)	0.127	14 (10.6)	111 (6.5)	0.074	6 (9.6)	52 (4.3)	0.051
Male gender	128 (68.5)	425 (54.6)	0.003**	92 (69.7)	968 (57.0)	0.004**	53 (85.5)	644 (53.8)	0.000**
MSAF	2 (1.1)	6 (0.8)	0.715	5 (3.8)	10 (0.6)	0.000**	11 (17.7)	28 (2.3)	0.000**
Increasing GA	82 (43.9)	179 (23.7)	0.000**	60 (45.5)	535 (31.5)	0.001**	15 (24.6)	361 (30.1)	0.075
	67 (35.8)	276 (36.6)		72 (54.5)	1164 (68.5)		12(19.4)	290 (24.2)	
	38 (20.3)	299 (39.7)					19 (30.6)	222 (18.5)	
							16 (26.4)	325 (27.1)	
Delivery mode									
CS without labor	104 (55.6)	293 (38.9)	0.000**	103 (78.0)	930 (54.7)	0.000**	32 (51.6)	600 (50.1)	0.542
CS with labor	54 (28.9)	200 (26.5)		17 (12.9)	450 (26.5)		6 (9.7)	107 (8.9)	
Vaginal delivery	29 (15.5)	261 (34.6)		12 (9.1)	319 (18.8)		24 (38.7)	491 (41.0)	

*$P < 0.05$, **$P < 0.01$. Abbreviations: PROM: Premature Rupture of Membranes; GDM: Gestational Diabetes Mellitus; PIH: Pregnancy induced Hypertension; MSAF: Meconium Stained Amniotic Fluid; GA: gestational age; CS: Cesarean Section.

Table 2. Multivariate logistic regression in infants of 34-36 weeks gestation

	OR	95% confidence interval		*P*-value
		(lower limit)	(upper limit)	
Gestational age (weeks)				
34	Reference			
35	0.35	0.22	0.61	0.000
36	0.19	0.11	0.30	0.000
PROM	1.92	1.25	3.54	0.038
Antenatal dexamethasone	0.18	0.12	0.36	0.000
GDM	3.43	1.64	6.87	0.000
Apgar Score < 7 at 5 min	3.28	1.67	5.85	0.008
Birth weight	0.42	0.29	0.63	0.028
Male gender	2.17	1.18	3.62	0.012
Placental abnormalities	1.85	1.03	3.40	0.043
Delivery mode				
Vaginal delivery	Reference			
CS without labor	4.28	2.63	7.12	0.000
CS with labor	3.30	1.98	5.63	0.000

Abbreviations: PROM: premature rupture of membrane; GDM: Gestational Diabetes Mellitus; CS: Cesarean Section.

mode were also significant risk factors for 37-38 week newborns. Fetal distress occurred more frequently in the RDS group compared with the controls in the 39-42 weeks group (22.6% *vs.* 5.4%, $P < 0.01$).

Multiple-factor analysis showed that gestational age and delivery mode are independent factors for infants of 34-36 and 37-38 weeks GA

Gestational diabetes and an Apgar score < 7 at 5 min post-birth were found to be independent risk factors for RDS in all three gestational age groups, where other factors differed for each group, as shown in **Tables 2**-**4**. For late preterm neonates (GA 34-36 weeks), the administration of antenatal dexamethasone, an independent factor for a favorable outcome, can significantly reduce the incidence of RDS (adjusted OR = 0.18, 95% CI = 0.12-0.36). The incidence of RDS rapidly decreased with increasing GA. Compared with infants born at 34 weeks of gestation, the OR of infants at 35 and 36 weeks were 0.35 and 0.19, respectively. The increasing birth weight also shown to be a positive effect on the development of RDS with increasing GA (OR = 0.42, 95% CI = 0.29-0.63). Cesarean section, particularly cesarean without labor, exerted a significant negative impact on the disease (adjusted OR = 4.28, 95% CI = 2.63-7.12). The effects of ge stational age and delivery mode were also apparent in neonates of 37-38 weeks (**Table 3**). MSAF was a significant risk factor for early full-term ($37^{0/7}$-$38^{6/7}$ weeks) and mature full-term infants ($39^{0/7}$-$42^{0/7}$ weeks) (OR = 5.92 and 13.6, respectively). Notably, Apgar < 7 at 5 min post-birth, male gender and GDM were the independent risk factors for all the three groups.

As shown in **Tables 3** and **4**, among the independent risk factors, fetal distress and umbilical cord abnormalities were the independent factors for 39-42 weeks infants, but not for infants of 37-38 weeks. In addition, delivery mode exerted a remarkable effect only shown in neonates of 37-38 weeks GA, but not for the infants of 39-42 weeks GA (**Table 3**).

Discussion

Respiratory Distress Syndrome (RDS) is associated with multiple neonatal and maternal factors, as well as environmental and social factors. Some studies have shown race to be an important factor in RDS [5]. In our study, 98.4% of all the participants were Han newborns from the same province in China; therefore, racial differences were not accounted for in this work. This study investigated risk factors for RDS, other than race, in Chinese neonates of 34-42 weeks GA. In this study, univariate and regression analysis of three GA groups showed that an Apgar score < 7 at 5 min post-birth, male gender, and gestational diabetes (GDM) were independent risk factors for all three GA groups. It has been shown that in infants less than 34 weeks of GA, GDM can adversely affect fetal lung development and maturity [12]. However, the effect of GDM on late preterm and full-term infants is less clear [13], possibly due to the different mechanisms underlying RDS. In infants of less than 34 weeks of GA, the primary mechanism involves surfactant synthesis; however, this does not explain the pathogenesis of RDS

Table 3. Multivariate logistic regression in infants of 37-38 weeks gestation

	OR	95% confidence interval		*P*-value
		(lower limit)	(upper limit)	
Gestational age (weeks)				
37	Reference			
38	0.59	0.40	0.85	0.005
GDM	3.82	2.14	6.83	0.000
Apgar Score < 7 at 5 min	4.33	1.93	9.71	0.000
MSAF	5.92	1.93	18.15	0.002
Male gender	1.73	1.17	2.58	0.006
Delivery mode				
Vaginal delivery	Reference			
CS without labor	3.76	1.86	7.58	0.000
CS with labor	1.49	0.65	3.44	0.347

Abbreviations: GDM: Gestational Diabetes Mellitus; CS: Cesarean Section.

Table 4. Multivariate logistic regression in infants of 39-42 weeks gestation

	OR	95% confidence interval		*P*-value
		(lower limit)	(upper limit)	
GDM	4.78	1.74	13.15	0.002
Apgar Score < 7 at 5 min	4.61	1.95	10.93	0.001
Umbilical cord abnormalities	3.24	1.25	5.38	0.013
MSAF	13.60	3.05	60.76	0.001
Male gender	5.15	2.47	10.76	0.000
Fetal distress	6.64	3.31	13.34	0.000

Abbreviations: GDM: Gestational Diabetes Mellitus; MSAF: Meconium Stained Amniotic Fluid.

in infants ≥ 34 weeks of GA. Male gender is a known risk factor for neonatal RDS for both preterm infants and term babies [15, 16]. To our knowledge, it is mainly ascribed to estrogen which positively regulates surfactant protein synthesis and induces some growth factors during the fetal period [17].

An Apgar score of < 7 at 5 min post-birth indicates poor conditions after delivery. In this case, respiratory function may be impaired and may exacerbate hypoxia. Hypoxic injury is now considered one of the more important risk factors for full-term infants with RDS, because the pathogenesis of RDS may be relevant to decreased PS activity caused by lung injury or edema [6, 7]. Our results imply that an Apgar score of < 7 at 5 min post-birth played an enhanced negative role on the development of RDS for the infant in the increasing GA group (OR = 3.28, 4.33, 4.61, respectively). In addition to the common risk factors, we also focused on the comparison of different risk factors in the three GA segments.

Antenatal dexamethasone administration for late preterm infants was associated with an 80% decrease in the incidence of RDS (OR = 0.18, 95% CI = 0.12-0.36). With improved pregnancy monitoring and assisted reproductive technology, late-preterm births have increased significantly over the last 30 years [2, 14]. Because the incidence of respiratory and neurological disorders is substantially higher than in full-term infants, this GA segment has garnered increased interest [15]. In our study, the incidence of RDS in late preterm infants was 19.9%. Lung development of the terminal alveoli and respiratory sacs continues through gestational weeks 34 and 36 [18]. Immaturity of the lungs results in an increased risk of RDS, although the administration of antenatal steroids may decrease morbidity by promoting lung maturity. Currently, there are mixed data regarding the effects of antenatal steroids on late preterm infants. A large clinical trial showed that administration of antenatal steroids for women at risk of late preterm delivery significantly reduced the rate of neonatal respiratory complications [19]. However, a placebo-controlled, randomized trial found no benefit to administering steroids to women between 34-36 weeks GA who are at risk of imminent premature delivery [20]. Our results suggest that the administration of antenatal dexamethasone can significantly reduce the risk of RDS for late preterm infants, with no statistically significant benefit to term infants. Based on this, we may recommend the administration of antenatal steroids for women at risk for late-preterm delivery to prevent RDS, not only for the unavoidable early-preterm delivery. However, the potential short or long-term neurodevelopmental effects, or other safety considerations

of steroid administration were not evaluated in this study. Whether antenatal steroid administration can significantly and safely reduce RDS in late preterm infants still requires further clinical investigation [21].

Further, cesarean delivery was a risk factor for RDS in the 34-36 and 37-38 weeks GA groups, but not in infants of 39-42 weeks. Our results align with the Europe 2016 guidelines on the management of Neonatal Respiratory Distress Syndrome [22], which recommend that elective cesarean sections without labor should be delayed until after 39 weeks. The effects of cesarean delivery on the respiratory system is mainly due to insufficient lung fluid clearance [23, 24]. During vaginal delivery, lung fluid is transferred from the alveolar space to the interstitial lung by alveolar Epithelial Na(+) channels (ENaCs) [25]. Antenatal steroid administration is one of the most effective means of promoting lung fluid absorption for late preterm and term infants [21, 22]. The mechanisms underlying this effect involve increased ENaCs RNA synthesis and β-adrenergic receptors, which contribute to the synthesis of surfactant and alveolar fluid absorption [21]. Cesarean delivery has been considered a risk factor for increasing respiratory morbidity [26]. Future studies will focus on the value of antenatal steroid administration for 34-38 weeks infants delivered by cesarean section.

In neonates of 34-36 and 37-38 weeks of GA, increasing gestational age was found to be a favorable factor against the development of RDS. These findings were consistent with those previous studies. An American study [15] of 19,334 cases of late preterm infants up to 38 weeks of gestation from 12 clinical units between 2002 and 2008 found that the incidence of respiratory system diseases, such as RDS, transient apnea, pneumonia, and respiratory failure, decreased with gestational age. Similarly, another large-scale study showed that CS increased the risk of RDS in infants of 37-38 weeks gestation significantly more than in 39 weeks infants [27]. These data are consistent with our results and confirm that in the absence of clinical indications for earlier delivery, pregnancy should be allowed to continue to 39 weeks before CS is performed.

In summary, an Apgar score < 7 at 5 min postbirth, male gender, and gestational diabetes are independent risk factors of RDS for late preterm and term Chinese infants. For 34-38 week newborns, the incidence of RDS decreases with advancing gestational age. However, cesarean delivery has a negative effect, particularly when it is performed without labor. In addition, antenatal dexamethasone administration can reduce the incidence of RDS for late preterm infants. These findings may assist those who manage the obstetric and pediatric care of Chinese neonates worldwide.

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Disclosure of conflict of interest

None.

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