Evidence to support that spontaneous preterm labor is adaptive in nature: neonatal RDS is more common in "indicated" than in "spontaneous" preterm birth

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Abstract

Objectives—The onset of preterm labor has been proposed to have survival value and to be adaptive in nature. This hypothesis would predict that induced preterm birth may be associated with higher rates of complications than spontaneous preterm birth. The purpose of this study was to determine if there is a difference in the frequency of neonatal respiratory distress syndrome (RDS), the most common neonatal complication, according to the etiology of preterm birth (e.g. preterm labor [PTL], preterm PROM, or pregnancies which ended because of maternal-fetal indications).

Study design—The relationship between the occurrence of RDS and the obstetrical circumstances leading to preterm birth was examined in 257 consecutive singleton preterm births (gestational age: 24-32 weeks). Cases with major congenital anomalies were excluded. The study population was divided into two groups according to the cause of preterm birth: 1) preterm birth due to PTL with intact membranes or preterm PROM (spontaneous preterm birth group); and 2) preterm birth due to maternal or fetal indications (indicated preterm birth group).

Results—1) RDS was diagnosed in 47% of cases; 2) RDS was more common in patients with indicated preterm birth than in those with spontaneous preterm birth group (58.1% vs. 38.4%, p=. 002); 3) Patients with indicated preterm birth had a significantly higher mean gestational age at birth, but lower mean birth weight, lower rate of histological chorioamnionitis and higher rates of cesarean delivery, 5 min Apgar score of <7, and umbilical arterial blood pH of <7.15 than those with spontaneous preterm birth (p<0.05 for each); 4) Antenatal corticosteroids were used in 73.4% of cases with indicated preterm birth and in 76.9% of those with spontaneous preterm birth; 5) Multivariate analysis demonstrated that indicated preterm birth was associated with an increased risk of RDS after adjustment for confounding variables (OR=2.29, 95% CI 1.22-4.29).

Conclusions—1) The rate of RDS is greater following "indicated" rather than spontaneous preterm birth; 2) This observation supports the view that spontaneous preterm labor is adaptive in nature.

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Keywords

Indicated preterm birth; neonatal respiratory distress syndrome (RDS); spontaneous preterm birth

Introduction

Preterm birth can result from spontaneous preterm labor with intact or rupture of membranes, or medically indicated preterm birth [2,19,21]. Among all singleton preterm births, spontaneous preterm births account for 65-70%, while 30-35% are due to indicated preterm delivery [1,10].

The onset of spontaneous preterm birth has been proposed to have survival value and to be adaptive in nature. This hypothesis predicts that induced or indicated preterm birth may be associated with higher rates of complications than spontaneous preterm birth.

Neonatal respiratory distress syndrome (RDS) is the most common complication and the leading cause of neonatal mortality in preterm newborns. In neonates born at 28-30 weeks of gestation, the prevalence of RDS can be as high as 70% [12]. Neonatal RDS occurs in one-fifth of low birth-weight babies (<2,500gm) and two-thirds of very low birth-weight infants (<1,500gm) [20].

The purpose of this study was to determine if there is a difference in the frequency of neonatal RDS, as a function of the etiology of preterm birth (e.g. preterm labor [PTL], preterm PROM, or maternal-fetal indications).

Materials and Methods

Study design

A retrospective cohort study was conducted to examine the difference in the occurrence of RDS according to the etiology of preterm birth. The study population consisted of 257 consecutive patients who delivered preterm singleton live-born neonates (gestational age at birth: 24-32 weeks) in the participating institution from January 1998 to December 2006. Forty-two cases with chromosomal abnormalities or major congenital anomalies were excluded from this study. Neonates were divided into two groups according to the cause of preterm birth: 1) preterm birth due to PTL with intact membranes or preterm PROM (spontaneous preterm birth group); and 2) preterm birth due to maternal or fetal indications (indicated preterm birth group).

Clinical characteristics of the patients and diagnosis of RDS

We reviewed the medical records to determine the clinical and demographic characteristics of the mothers and their neonates. The demographic characteristics included age, parity and gestational age at delivery. Clinical characteristics consisted of antenatal corticosteroid administration, histopathological diagnosis of the placenta, and whether or not a cesarean delivery was performed. We also included gender, 1 minute Apgar score, 5 minute Apgar score, and umbilical arterial blood gas analysis. The Institutional Review Board of the Seoul National University approved the medical records review for this study.

Histological chorioamnionitis was defined as the presence of acute inflammatory changes in a membrane roll and the chorionic plate of the placenta. Funisitis was diagnosed in the presence of neutrophil infiltration into the umbilical vessel walls or Wharton's jelly using criteria previously published and used in our studies [27].

The primary outcome variable was the presence of RDS in the newborn which was defined as the presence of respiratory distress, increased oxygen requirement (FiO$_2$>0.4), and diagnostic radiological and laboratory findings in the absence of evidence of any other causes of respiratory distress.

Statistical analysis

The Mann-Whitney U test or Student's t test was used for the comparison of the continuous variables. For the dichotomized variables, χ^2 test or Fisher's exact test was performed. Multiple logistic regression analysis was used to examine the relationship between the etiology of preterm birth and the occurrence of RDS, controlled for the effect of potential confounding variables.

Results

Two hundred and fifty-seven mothers and their neonates met the entry criteria and 14 cases were excluded because the neonates died immediately after birth despite resuscitation. RDS was diagnosed in 47% (114/243) of newborns.

Table 1 describes the clinical and demographic characteristics of the study population according to the etiology of preterm birth. No significant differences were found in the maternal age, parity and the rate of the antenatal corticosteroid administration between the indicated preterm birth group and the spontaneous preterm birth group. Neonates in the indicated preterm birth group had a significantly higher mean gestational age at delivery, but lower mean birthweight than those in the spontaneous preterm birth group. Newborns who were delivered because of maternal and/or fetal indications had a significantly lower rate of histological chorioamnionitis and higher rates of cesarean delivery, 5 minute Apgar score of <7 and umbilical arterial blood pH of <7.15 than those who were delivered due to spontaneous labor or preterm PROM. There was no difference in neonatal mortality between the two groups. The prevalence of RDS in the indicated preterm birth group was significantly higher than in the spontaneous preterm birth group (58.1% vs. 38.4%, p=.002).

Table 2 shows the characteristics of the neonates according to the presence or absence of RDS. Neonates who developed RDS were delivered at lower mean gestational ages, and had a lower mean birth weight than those without RDS. The rate of cesarean delivery in neonates with RDS was higher than in those without RDS. However, no significant difference was found in the rate of antenatal corticosteroid use between the two groups. Babies with RDS had significantly higher rates of 1 minute and 5 minute Apgar scores of <7 and umbilical arterial blood pH of <7.15 than those without RDS. The frequencies of histological chorioamnionitis and funisitis in neonates with RDS were significantly lower than in those without RDS.

Using multiple logistic regression to adjust for the effect of gestational age at delivery, indicated preterm birth was associated with an increase in the odds ratio (OR) for the development of RDS (OR=3.16; 95% confidence interval (CI) 1.78-5.60; p <.001; Figure 1). The relationship remained significant (OR=2.29; 95% CI 1.22-4.29; p=.010; Table 3), even after adjusting for other variables that could have influenced the occurrence of RDS, such as cesarean delivery and antenatal corticosteroid use.

The frequency of RDS in the indicated preterm birth group was similar to that in the spontaneous preterm birth group among newborns delivered by cesarean section (58.2% vs. 47.2%, p=0.158) and also among newborns delivered vaginally (57.1% vs. 28.8%, p=.196). However, indicated preterm birth was significantly associated with the increase in the odds ratio for the development of RDS in both the cesarean and vaginal delivery groups, after the

adjusting for gestational age at delivery and antenatal corticosteroid use (p<0.05 for each, Table 4).

Discussion

Principal findings of the study

The rate of RDS in the indicated preterm birth group was significantly higher than in the spontaneous preterm birth group among preterm singleton neonates whose gestational age at birth was less than 32 weeks. This remained significant after adjusting for the effect of confounding factors which could affect the development of RDS, such as gestational age at delivery, antenatal corticosteroid use, and cesarean delivery.

Why should RDS be less frequent in cases of spontaneous rather than indicated preterm birth

One possible explanation is that the rate of histological chorioamnionitis was higher in spontaneous preterm labor/delivery than in indicated preterm birth. Bry et al [3,4] reported that intraamniotic interleukin-1 and endotoxin stimulate surfactant protein synthesis and lung maturation in fetal rabbits. Subsequently, many investigators [14-16,18,24] have demonstrated that chorioamnionitis accelerates fetal lung maturity. For example, Shimoya et al [24] reported that chorioamnionitis induces fetal lung maturation by increasing interleukin-6 and decreases the incidence of RDS. In this study, neonates born after spontaneous preterm birth had a significantly higher rate of histological chorioamnionitis than those in the indicated preterm birth group (59.9% vs. 9.3%; p<.001), and this relationship remained significant after adjusting for gestational age at delivery (adjusted OR=13.48; 95% CI 6.20-29.28).

Should preeclampsia decrease the rate of RDS after an indicated preterm birth?

Traditionally, it has been believed that chronic intrauterine stress such as preeclampsia, accelerates fetal lung maturity [5,23]. However, recent studies [6,22,26] indicate that this may not be the case. Moreover, Chang et al [7] observed that the risk of RDS in neonates at <32 weeks of gestation is increased in mothers with preeclampsia. In this study, there was a trend towards a higher rate of RDS in newborns whose mothers had a hypertensive disorder compared to those whose mothers were normotensive during pregnancy (55.6% vs. 42.6%; p=.056), although it was not statistically significant. The percentage of those with a hypertensive disorder in the indicated preterm birth group was higher than in the spontaneous preterm birth group (74.5% vs. 2.7%). This point could explain the higher rate of RDS in the indicated preterm birth group.

Results of other studies

Our findings are in keeping with those of a large population-based study [17], even though this study did not adjust for confounding factors, except for gestational age at birth, which could have influenced the occurrence of RDS. The authors [17] reported that "indicated preterm birth" was associated with both neonatal respiratory and gastrointestinal diseases, which may decrease survival.

In preterm twin gestations, several investigators [11,25] have observed that second twins have higher rates of RDS, chronic lung disease and neonatal mortality than first twins. In preterm PROM, the first twin is more likely to be exposed to the effect of microbial products and cytokines than the second twin, and this may be an explanation for these findings.

In this study, spontaneous preterm labor with intact membranes, preterm PROM, and preterm birth due to maternal/fetal indications accounted for 32.7%, 24.5%, and 42.8% of total preterm births before 32 weeks of gestation. The frequency of indicated preterm birth was relatively

high in our study compared with previous reports [1,10]. However, this probably reflects the fact that the study population was restricted to a gestational age at birth of 24-32 weeks.

Roberts and Dalziel [20] have demonstrated that antenatal corticosteroid administration to mothers with impending preterm delivery decreases the occurrence of RDS. However, this effect did not reach statistical significance in our study (adjusted OR 0.67; 95% CI 0.35-1.29; p=.226). One explanation for this finding is a selection bias because of the small size of population studied or a suboptimal effect because of an incomplete course of corticosteroids [8,9,13].

In conclusion, the rate of RDS is greater in "indicated" rather than in spontaneous preterm birth. This observation supports the view that spontaneous preterm labor is adaptive in nature.

Acknowledgments

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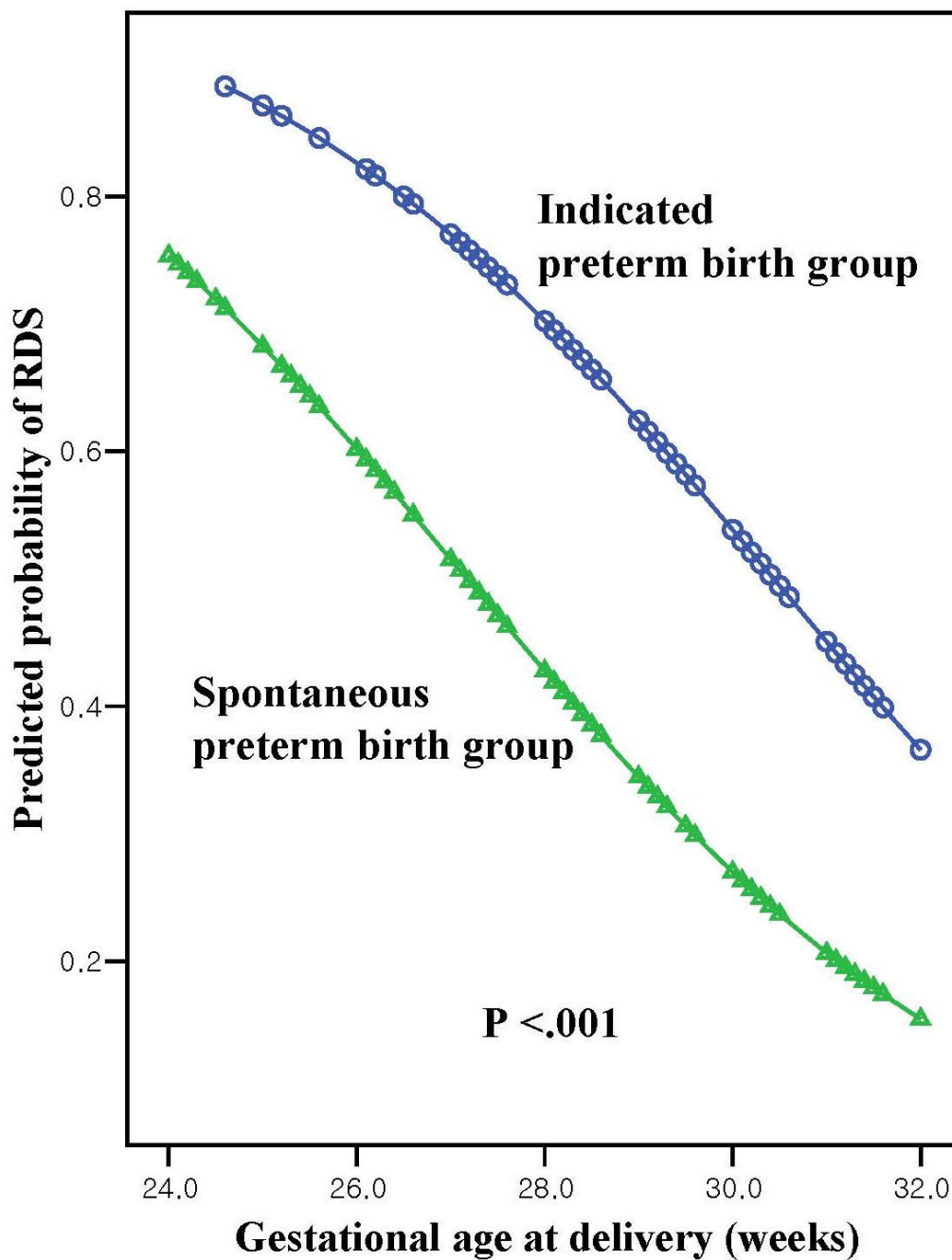
Figure 1.
Plot of predicted probability of RDS according to the gestational age at delivery and etiology of preterm birth. [After adjusting for gestational age at delivery, indicated preterm birth increased the odds of development of RDS (adjusted OR=3.16; 95% CI 1.78-5.60; p <.001)].

Table 1

Characteristics of the study population according to the etiology of preterm birth

	Indicated preterm birth group (n=110)	Spontaneous preterm birth group (n=147)	P value
Maternal age (mean±SD)	32.0±4.5	31.3±4.4	NS
Parity (nulliparity) (%)	47.3 (52/110)	47.6 (70/147)	NS
Gestational age at delivery (weeks) (mean±SD)	29.3±1.8	28.5±2.3	.005
Antenatal steroid use[*] (%)	73.4 (80/109)	76.9 (113/147)	NS
Cesarean delivery (%)	91.8 (101/110)	51 (75/147)	<.001
Sex (Male) (%)	40.9 (45/110)	64.6 (95/147)	<.001
Birth weight (g) (mean±SD)	1069.7±401.7	1286.9±408.0	<.001
1-min Apgar score of < 7 (%)	84.5 (93/110)	76.9 (113/147)	NS
5-min Apgar score of < 7 (%)	64.5 (71/110)	49.7 (73/147)	.017
Umbilical arterial pH of < 7.15[†] (%)	25.3 (25/99)	10.1 (13/129)	.002
Hypertensive disorders (%)	74.5 (82/110)	2.7 (4/147)	<.001
Histological chorioamnionitis[‡] (%)	9.3 (9/97)	59.9 (82/137)	<.001
Funisitis[§] (%)	1.0 (1/98)	33.8 (47/139)	<.001
RDS[¶] (%)	58.1 (61/105)	38.4 (53/138)	.002
Neonatal mortality (%)	16.4 (18/110)	11.6 (17/147)	NS

NS, not significant; *RDS*, respiratory distress syndrome.

[*] One case was excluded from the analysis because of unavailable data for the use of antenatal corticosteroid.

[†] Twenty-nine cases that did not have the results of the umbilical arterial blood gas analysis were excluded from the analysis.

[‡] Twenty-three cases that did not have histopathologic examinations of the placenta were excluded from the analysis.

[§] Twenty cases that had unavailable placental histological results for funisitis were excluded from the analysis.

[¶] Fourteen cases that died immediately at the delivery room regardless of resuscitation were excluded from the analysis.

Table 2

Clinical characteristics of patients according to occurrence of neonatal RDS

	RDS (−) (n=129)	RDS (+) (n=114)	P value
Maternal age (mean±SD)	31.5±4.2	31.7±4.7	NS
Parity (nulliparity) (%)	49.5 (64/129)	45.6 (52/114)	NS
Gestational age at delivery (weeks) (mean±SD)	29.5±1.9	28.4±2.1	<.001
Antenatal steroid use (%)	80.6 (104/129)	71.9 (82/114)	NS
Cesarean delivery (%)	61.2 (79/129)	79.8 (91/114)	.002
Sex (Male) (%)	52.7 (68/129)	53.5 (62/114)	NS
Birth weight (g) (mean±SD)	1281.5±411.4	1146.9±403.7	.007
1-min Apgar score of < 7 (%)	68.2 (88/129)	92.1 (105/114)	<.001
5-min Apgar score of < 7 (%)	40.3 (52/129)	68.4 (78/114)	<.001
Umbilical arterial pH of < 7.15[*] (%)	9.8 (11/112)	23.6 (25/106)	.006
Hypertensive disorders (%)	27.9 (36/129)	39.5 (45/114)	.056
Histological chorioamnionitis[†] (%)	46.7 (56/120)	28.7 (31/108)	.005
Funisitis[‡] (%)	25.4 (31/122)	13.8 (15/109)	.027

[*] Twenty-five cases that did not have the results of the umbilical arterial blood gas analysis were excluded from the analysis.

[†] Fifteen cases that did not have histopathologic examinations of the placenta were excluded from the analysis.

[‡] Twelve cases that had unavailable placental histological results for funisitis were excluded from the analysis.

Table 3

Relationship of various variables with the occurrence of RDS analyzed by overall logistic regression

	Odds ratio	95% confidence interval	*P* value
Gestational age at delivery	0.70	0.60-0.81	<.001
Indicated preterm birth	2.29	1.22-4.29	.010
Cesarean delivery	2.26	1.13-4.53	.022
Antenatal corticosteroid use	0.67	0.35-1.29	.226

Table 4

Comparison of the occurrence of neonatal RDS according to the etiology of preterm birth and mode of delivery

	Indicated preterm births	Spontaneous preterm births	P- value	
			Unadjusted	Adjusted[*]
Among cases with cesarean delivery	(n=101)	(n=75)		
Gestational age at delivery (weeks) (mean±SD)	29.4±1.8	28.7±2.1	.055	
Antenatal steroid use[†] (%)	74.0 (74/100)	77.3 (58/75)	NS	
RDS[‡] (%)	58.2 (57/98)	47.2 (34/72)	.158	.048
Among cases with vaginal delivery	**(n=9)**	**(n=72)**		
Gestational age at delivery (weeks) (mean±SD)	28.9±2.6	28.2±2.5	.363	
Antenatal steroid use (%)	66.7 (6/9)	76.4 (55/72)	NS	
RDS[§] (%)	57.1 (4/7)	28.8 (19/66)	.196	.033

NS, not significant; *RDS*, respiratory distress syndrome.

[*] By logistic regression, adjusted for gestational age at delivery and antenatal corticosteroid use.

[†] One case was excluded from the analysis because of unavailable data for the use of antenatal corticosteroid.

[‡] Six cases that died immediately at the delivery room regardless of resuscitation were excluded from the analysis.

[§] Eight cases that died immediately at the delivery room regardless of resuscitation were excluded from the analysis.