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Neonatal Respiratory Morbidity after Late Preterm, Singleton, Cesarean Delivery before Labor by Mothers Who Did Not Receive Antenatal Corticosteroids

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Background: Some evidence suggests that administration of antenatal corticosteroids (ACS) reduces neonatal respiratory complications among women at risk for late preterm birth. However, because of concerns regarding long-term outcomes of children, ACS is not recommended in Japan for pregnant women at risk in late preterm. We assessed the risk of neonatal respiratory morbidity after late preterm, singleton, cesarean delivery before labor by mothers who did not receive ACS.

Methods: We retrospectively reviewed and analyzed data on singleton cesarean deliveries of late preterm infants. The prevalence of neonatal respiratory morbidity requiring ventilatory support, such as continuous positive airway pressure or mechanical ventilation, was analyzed in relation to gestational age in late preterm. Respiratory distress syndrome (RDS) in neonates was also evaluated.

Results: We analyzed data from 100 late preterm, singleton, cesarean deliveries: 22 neonates were delivered at 34 weeks, 34 at 35 weeks, and 44 at 36 weeks. Respiratory morbidity significantly decreased in relation to gestational age ($p < 0.001$). Similarly, there was a significant difference in RDS, which was most frequent at 34 weeks (18.2%, $p = 0.017$). There were no cases of RDS at 36 weeks.

Conclusion: Late preterm, singleton, cesarean delivery before labor in mothers who did not receive ACS was associated with a need for ventilation, especially for infants born at 34 and 35 weeks. ACS treatment might therefore be beneficial before elective cesarean section for mothers with a risk of preterm delivery before 35 weeks and 6 days. (J Nippon Med Sch 2022; 89: 580–586)

Key words: adrenal cortex hormones, cesarean section, delivery of health care, pregnancy, premature birth

Introduction

The rate of preterm birth is increasing in industrialized countries[1,2], and late preterm birth, defined as delivery between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, accounts for a large proportion of overall preterm births—approximately 70% of preterm births in high-income countries[1]. The incidence of late preterm births is also increasing in Japan[2]. A recent population-based study found that neonatal morbidity for late preterm infants was seven times that for term infants[3]. A cohort study reported that, as compared with term delivery, late preterm birth was associated with increased risks of respiratory morbidities, such as respiratory distress syndrome (RDS)[4]. In particular, late preterm birth by cesarean section before labor was associated with greater respiratory morbidity[5,6].

Antenatal corticosteroid (ACS) administration at 24-34 weeks of gestation, among mothers with a risk of preterm delivery within 7 days, reduced the incidence of neonatal morbidity from RDS in preterm infants[7,8]. Moreover, some obstetric practice guidelines, including those published in Japan, recommend administering a single course of ACS between $24^{0/7}$ weeks and $33^{6/7}$ weeks to

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https://doi.org/10.1272/jnms.JNMS.2022_89-612
Journal Website (https://www.nms.ac.jp/sh/jnms/)

women who are at risk of preterm delivery within 7 days[9–12]. A randomized controlled trial (RCT) found that ACS reduced respiratory complications among neonates of women at risk for late preterm delivery[13]. The American College of Obstetrician and Gynecologists (ACOG) committee and other national obstetric practice guidelines recommend administering ACS to women at risk of late preterm delivery within 7 days[9,10,14]. However, since the long-term outcomes of infants born to women who received ACS in late preterm before labor remain unclear, this recommendation remains controversial. Therefore, the Japanese obstetric practice guideline does not recommend ACS for pregnant women at risk of late preterm delivery[11,12]. Additionally, there is no national health care insurance system guideline regarding ACS for pregnant women at risk for late preterm labor in Japan.

The objective of the study was to assess the risk of late preterm neonatal respiratory morbidity after singleton cesarean delivery before labor in women who did not receive ACS during pregnancy.

Methods

This retrospective cohort study analyzed data collected between January 2013 and June 2020 at a single center. The participants were women at 34 to 36 weeks of pregnancy with a singleton gestation who underwent cesarean section before labor at our hospital. The exclusion criteria were labor onset, receipt of complete ACS, congenital anomalies, and chromosomal abnormalities. Some studies reported favorable respiratory outcomes for neonates delivered by cesarean section after labor onset[15–17]. Therefore, labor-onset cases were excluded from the present study, to avoid the effect of labor on respiratory outcomes. Complete ACS cases were defined as receipt of 12 mg of betamethasone twice every 24 hours, with delivery within 7 days after betamethasone administration. The outcomes were neonatal respiratory morbidity and RDS after a late preterm birth. Neonatal respiratory morbidity was defined as need for ventilatory support, such as continuous positive airway pressure (CPAP) or mechanical ventilation in the neonatal intensive care unit (NICU). RDS was defined as need for intubation and surfactant therapy in the NICU. This study was approved by the Ethics Committee of Nippon Medical School Musashikosugi Hospital, and all patients provided informed consent before enrollment in the study (approval number: 583-2-48, January 5, 2021).

The following maternal data were collected from patients' clinical records: maternal age, body mass index (BMI) in early pregnancy, parity, smoking, and pregnancy with artificial reproductive technology (ART). Data were obtained on placenta previa, including total, partial, and marginal previa and low-lying placenta; hypertensive disorder of pregnancy; and placental abruption. Data were also collected on fetal growth restriction (defined as an estimated fetal weight of −1.5 SD), premature rupture of membrane complicated by breech presentation, nonreassuring fetal status, and uterine scarring by, for example, previous cesarean section and uterine surgery. On the basis of the last menstrual period (LMP), fetal crown-rump length (CRL) was measured in the first trimester; CRL was used when its measurement was inconsistent with that based on LMP.

The following neonatal data were obtained from clinical records: sex of newborns, small for gestational age (SGA) status, birth weight, APGAR score ≤7, umbilical cord arterial pH, NICU admission, and RDS (surfactant administration). Data on respiratory morbidity, respiratory device support (including intubation and CPAP), and duration of NICU stay were also collected. SGA was defined as a birth weight below the 10th percentile, according to standard neonatal weight charts for the Japanese population[18].

All data were analyzed by using one-way analysis of variance for continuous variables and the χ^2 test and Fisher exact test for qualitative variables among groups classified by gestational age. Continuous variables were analyzed with the Shapiro-Wilk test as a test of normality. All data analyses were performed with IBM SPSS Statistics 23. Statistical significance was set at $p < 0.05$.

Results

Our study included 6,316 deliveries, 2,102 of which were cesarean section deliveries (**Fig. 1**). There were 122 cases of cesarean section deliveries in late preterm infants. Twenty-two pregnant women were excluded from the study on the basis of the exclusion criteria. Among the remaining pregnant women, 22 neonates were delivered at 34 weeks of gestational age, 34 at 35 weeks, and 44 at 36 weeks. There were no significant differences in maternal age, BMI in early pregnancy, parity, smoking, or ART between groups (**Table 1**). **Table 2** shows the indications for cesarean delivery before labor by gestational age. Placenta previa was the most frequent indication at 36 weeks (38.6%, $p = 0.036$). **Table 3** summarizes neonatal outcomes by gestational age. There was a significant difference in respiratory morbidity by gestational age ($p < 0.001$) between groups: respiratory morbidity signifi-

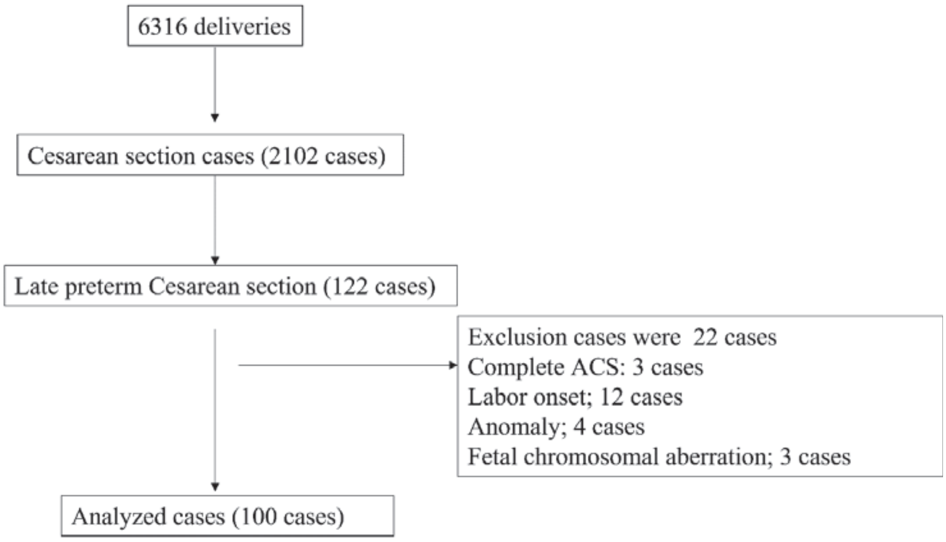

Fig. 1 Diagram showing numbers of included and excluded cases
ACS: antenatal corticosteroids

Table 1 Baseline maternal characteristics by gestational age

Gestational age (weeks + days of gestation)	34 + 0 ~ 34 + 6 (n = 22)	35 + 0 ~ 35 + 6 (n = 34)	36 + 0 ~ 36 + 6 (n = 44)	P value
Maternal age (years)	34.4 ± 5.17	33.5 ± 5.70	35.1 ± 4.25	NS
BMI in early pregnancy (Kg/m²)	21.2 ± 3.14	20.6 ± 3.42	21.5 ± 2.89	NS
Multiparity	11 (50.0)	12 (35.3)	21 (47.7)	NS
Smoking	1 (4.54)	0	0	NS
ART	2 (9.09)	3 (8.82)	8 (18.2)	NS

Data are presented as n (%). Continuous variables are shown as mean ± standard deviation
BMI: body mass index
ART: assisted reproductive technology

Table 2 Indications for cesarean delivery without labor by gestational age

Gestational age (weeks + days of gestation)	34 + 0 ~ 34 + 6 (n = 22)	35 + 0 ~ 35 + 6 (n = 34)	36 + 0 ~ 36 + 6 (n = 44)	P value
Placenta previa	4 (17.4)	7 (21.2)	17 (38.6)	0.036
HDP	4 (17.4)	9 (27.3)	11 (25)	0.469
FGR	3 (13.0)	6 (18.2)	6 (13.6)	0.595
Placental abruption	1 (4.35)	2 (6.06)	0	0.266
PROM	8 (34.8)	9 (27.3)	8 (18.2)	0.163

Data are presented as n (%)
Placenta previa is defined as total previa, partial previa, marginal previa, and low-lying placenta
HDP: Hypertensive disorders of pregnancy, FGR: fetal growth restriction
PROM: premature rupture of membrane included breech presentation, non-reassuring fetal status, and scarred uterus

cantly decreased with gestational age. Specifically, the respiratory morbidity rate was significantly higher at 34 weeks than at 35 weeks (40.9% vs. 11.8%, $p < 0.001$) and significantly higher at 35 weeks than at 36 weeks (11.8% vs. 2.27%, $p = 0.021$). Similarly, the incidence of RDS was significantly higher at 34 weeks (18.2%, $p = 0.017$); no case of RDS was noted at 36 weeks. Birth weight and hospital stay rate significantly differed in relation to gestational age ($p < 0.001$ and $p < 0.001$, respectively). We analyzed whether neonates between 34 and 35 weeks of

Table 3 Neonatal outcomes by gestational age

Gestational age (weeks + days of gestation)	34 + 0 ~ 34 + 6 (n = 22)	35 + 0 ~ 35 + 6 (n = 34)	36 + 0 ~ 36 + 6 (n = 44)	P value
Sex (male)	16 (72.7)	21 (61.8)	24 (54.5)	0.202
Birth weight (g)	1,971 ± 263	2,224 ± 340	2,413 ± 267	<0.001
SGA	4 (18.2)	8 (23.5)	4 (9.09)	0.095
Low Apgar score at 5 min (=<7)	1 (4.55)	0	0	0.220
Umbilical artery pH	7.305 ± 0.046	7.320 ± 0.042	7.312 ± 0.036	0.409
Respiratory morbidity	9 (40.9)	4 (11.8)	1 (2.27)	<0.001
RDS	4 (18.2)	3 (8.82)	0	0.017
hospital stay in NICU (days)	22 ± 9	15 ± 9	4 ± 6	<0.001

Data are presented as n (%), median (interquartile range). Continuous variables are shown as mean ± standard deviation
SGA: Small for gestational age, RDS; Respiratory distress syndrome, NICU: Neonatal intensive care unit
Respiratory morbidity was defined as indication for respiratory device support, including intubation and continuous positive airway pressure
RDS was defined as requirement of surfactant in the NICU.

Table 4 Neonatal respiratory complication per the indication for cesarean section delivery

Gestational age (weeks + days of gestation)	34 + 0 ~ 35 + 6 (n = 56)	36 + 0 ~ 36 + 6 (n = 44)	P value
Placenta previa and respiratory morbidity	5 (8.92)	1 (2.27)	0.065
Placenta previa and RDS	3 (5.36)	0	0.253
HDP and respiratory morbidity	2 (3.57)	0	0.502
HDP and RDS	2 (3.57)	0	0.502
FGR and respiratory morbidity	3 (5.36)	0	0.253
FGR and RDS	1 (1.79)	0	1.000
Placental abruption and respiratory morbidity	1 (1.79)	0	1.000
Placental abruption and RDS	1 (1.79)	0	1.000
PROM and respiratory morbidity	3 (5.36)	0	0.253
PROM and RDS	0	0	-

Data are presented as n (%)
Placenta previa is defined as total previa, partial previa, marginal previa, and low-lying placenta
RDS; Respiratory distress syndrome is defined as the requirement of surfactant in the NICU
HDP: Hypertensive disorders of pregnancy, FGR: fetal growth restriction
Respiratory morbidity is defined as indication for respiratory device support, including intubation and continuous positive airway pressure
PROM: Premature rupture of membrane included Breech presentation, non-reassuring fetal status, and scarred uterus.

gestational age were at risk of neonatal respiratory disorders, in relation to indications for cesarean delivery (**Table 4**). There was no significant difference in respiratory disorders in late preterm between infants delivered before 35 weeks 6 days and those delivered after 36 weeks; however, infants from cesarean births for placenta previa had a higher risk of respiratory morbidity, although the difference was not significant (8.92% vs. 2.27%, p = 0.065).

Discussion

In our study, the rate of respiratory morbidity in late preterm infants delivered by cesarean section before labor in the absence of complete ACS was highest at 34 weeks of gestational age and decreased significantly with increasing gestational age. There was also a significant difference in the incidence of RDS in late preterm infants: it was highest at 34 weeks of gestational age, and no cases were noted for infants born at 36 weeks of gestation. The risk of respiratory morbidity tended to be higher for neonates born at 34 weeks and 35 weeks to women with placenta previa than for those born at 36 weeks.

We found that, in the absence of complete ACS, neonates required ventilatory support and surfactant use after late preterm cesarean delivery before labor. In addition, the risk of neonatal respiratory morbidity after cesarean delivery before labor was significantly higher at 34 and 35 weeks of gestational age. A previous multicenter study in Japan reported that earlier delivery, as determined by gestational age in weeks at late preterm, and cesarean birth were independent risk factors for neonatal respiratory disorders, including need for mechanical ventilation and use of CPAP[19]. However, that study included late preterm infants from cesarean deliveries during labor. Other studies found that the risk of respiratory morbidity was higher after cesarean birth without labor than after labor onset[15–17]. A recent study suggested that there was a risk of respiratory disorders in late preterm infants after cesarean delivery before labor onset[20]. That retrospective study reported that the risk of respiratory disorder requiring ventilatory support or oxygen therapy significantly decreased as gestational age increased in late preterm infants. Although infants from multiple gestations were included in that study, infants delivered by emergency cesarean section without labor were excluded[20]. As was the case in some previous studies, our study showed that the risk of respiratory illness requiring ventilatory support or surfactant use was significantly higher for late preterm infants from singleton cesarean deliveries before labor. Conversely, significantly fewer late preterm infants were delivered at 36 weeks. These results suggest that neonates delivered before 35 weeks 6 days of gestational age had a much higher risk for respiratory morbidity.

In our study, respiratory morbidity of neonates after cesarean birth due to placenta previa was higher between 34 weeks and 35 weeks 6 days. A previous study reported that for deliveries after 20 weeks of gestation, neonates born to pregnant women with placenta previa had a significantly higher rate of preterm delivery and a higher incidence of RDS[21]. A study that compared outcomes for neonates born to women with placenta previa at 35 to 37 weeks of gestation with those born to women without placenta previa who underwent cesarean section at 38 weeks reported significantly more cases of NICU admission and APGAR scores ≤7 in the placenta previa cases at 35 to 36 weeks of gestation[22]; however, there was no significant difference in need for respiratory device support or RDS[22]. We found no significant difference in respiratory morbidity in neonates born to pregnant women with placenta previa, perhaps because of the small number of such cases. Cesarean delivery for placenta previa in the late preterm, especially before 35 weeks 6 days, might be a risk for neonatal respiratory morbidity.

ACS during pregnancy may improve short-term respiratory outcomes of neonates born to women at risk for late preterm delivery. A recent multicenter RCT reported that ACS significantly reduced respiratory failure requiring CPAP, high-flow nasal cannula oxygen, ventilatory management, or extracorporeal membrane oxygenation (ECMO) within 72 hours of birth in late preterm infants (risk ratio, 0.68; 95% confidence interval, 0.47-0.98)[13]. In addition, a recent systematic review of seven RCTs examining late preterm infants found that ACS significantly reduced respiratory impairment requiring ventilatory management[23]. Therefore, ACOG and other practice guidelines recommend administration of ACS to pregnant women at risk of preterm delivery at 34-36 weeks gestation within 7 days[9,10,14]. However, in a large cohort study of 670,000 Finnish participants, ACS was significantly associated with mental and behavioral disorders in term-born children of mothers treated with ACS. This was found during long-term follow-up (adjusted hazard ratio, 1.47; 95% confidence interval, 1.36-1.69; median duration of follow-up, 5.8 years, interquartile range, 3.1-8.7)[24]. Interestingly, this population-based study also showed that mental and behavioral disorders in preterm-born children were not significantly different between groups with and without ACS (adjusted hazard ratio 1.00; 95% confidence interval 0.92-1.09). However, late preterm birth, especially at 34 weeks of gestation, might be a risk for poor long-term respiratory outcomes in children. A longitudinal study reported that forced expiratory spirometry at age 8-9 years was lower in children born at 33-34 weeks of gestation than in those born at term and was similar to that in an extremely preterm (25-32 weeks gestation) group[25]. That study found that children requiring mechanical ventilation at 25-32 and 33-34 weeks of gestational age had worse airway function than did those who were not ventilated. In contrast, children born at 35-36 weeks of gestational age had lung function equivalent to that of term-born controls at age 8-9 and age 14-17.

Japanese practice guidelines do not recommend ACS for women at late preterm, because of lingering concerns regarding long-term adverse events in children treated with ACS[11,12]. In our study, respiratory morbidity in neonates after cesarean delivery without labor onset was higher before 35 weeks and 6 days of gestational age in mothers not receiving ACS. In addition, the need for ventilators tended to be higher for neonates delivered at 34 to 35 weeks 6 days by cesarean section because of placenta previa than for those delivered at 36 weeks. This finding might be controversial because long-term outcomes are unclear for neonates born to mothers at risk of late preterm birth who received ACS. However, because maternal pregnancy complications such as placenta previa tend to affect early respiratory outcomes in infants after late preterm cesarean deliveries before labor, our results suggest that ACS treatment may be beneficial for women at high risk of preterm delivery before 35 weeks 6 days, especially preterm deliveries caused by placenta previa.

A limitation of our study is that it was a retrospective study of a small sample. Furthermore, the late preterm cesarean section cases included patients at high risk for respiratory complications, such as hypertensive disorder of pregnancy, placental abruption, and fetal growth restriction, perhaps because our hospital is a regional perinatal center and treats many high-risk patients. Further prospective cohort studies with a greater number of cases are required in order to validate our findings.

In conclusion, when ACS was not administered, late preterm birth after cesarean delivery before labor—especially at 34 weeks and 35 weeks of gestational age—was associated with a need for ventilation or CPAP in neonates. ACS treatment might reduce the risk of respiratory morbidity in neonates of women undergoing elective cesarean section who are at risk of preterm delivery before 35 weeks 6 days of gestational age.

Acknowledgements: The authors would like to thank Eika Harigane, MD, Go Ichikawa, MD, Ph.D., Asako Watanabe, MD, Kouren Shi, MD, Mayu Yamada, MD, and Ayako Takizawa, MD, from the Department of Obstetrics and Gynecology at Nippon Medical School Musashikosugi Hospital.

Conflict of Interest: None.

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(Received, April 18, 2022)
(Accepted, June 1, 2022)
(J-STAGE Advance Publication, October 21, 2022)