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MATERNAL-FETAL MEDICINE

Respiratory morbidity in late preterm twin infants

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Abstract

Purpose Antenatal corticosteroids have been shown to decrease neonatal respiratory morbidity in singleton pregnancies when given during the late-preterm period ($34^{0/7}$–$36^{6/7}$ weeks). Whether these findings also apply to late-preterm twins, who account for approximately one-third of infants born at $34^{0/7}$–$35^{6/7}$ weeks, is currently unclear. The answer to this question depends, in part, on whether the risk of respiratory morbidity among late-preterm twin infants is similar to that observed in late-preterm singletons. We aimed to assess the rate of respiratory morbidity among late-preterm twin infants using a secondary analysis of prospectively collected data from a large international multicenter trial, and to compare that rate with previous studies that used the same definition of respiratory morbidity.

Study design This was a secondary analysis of the twin birth study. In the current study, we limited the analysis to women who gave birth during the late preterm period. The primary outcomes were the same primary composite respiratory morbidity variables that were used in the randomized controlled trial of Gyamfi-Bannerman et al., on the administration of betamethasone during the late preterm period in singletons (ALPS trial). The risk of respiratory morbidity among late preterm twins was stratified by gestational week at birth.

Results A total of 1163 women who gave birth to 2324 late preterm twin infants met the inclusion criteria. The rates of respiratory morbidity and severe respiratory morbidity were 16.5% and 8.9%, respectively. The risk of respiratory morbidity was highly dependent on gestational week at birth, being more than fourfold for infants born at $34^{0/7}$–$34^{6/7}$ weeks (aOR 4.30, 95%–CI 3.01–6.14) and more than twofold for infants born at $35^{0/7}$–$35^{6/7}$ weeks (aOR 2.12, 95%–CI 1.51–2.98) compared with infants born at $36^{0/7}$–$36^{6/7}$ weeks. The rate of respiratory morbidity and the theoretical number of women needed to be treated with betamethasone to prevent a single case of respiratory morbidity in the current study were similar to those reported in the APLS trial (16.5% vs. 14.4%, $p=0.103$, and NNT 31 vs. 34, respectively).

Conclusions The risk–benefit ratio of betamethasone with regard to neonatal respiratory morbidity in women with twins at risk of late-preterm birth is expected to be similar to that observed in singletons.

Keywords Betamethasone · Corticosteroids · Late-preterm · Multifetal · Steroids · Twins

Introduction

Late prematurity, defined as preterm birth between $34^{0/7}$ and $36^{6/7}$ weeks of gestation, accounts for 60–70% of preterm births [1, 2] and is associated with an increased risk of neonatal mortality and morbidity [1, 3, 4]. A recent randomized controlled trial by Gyamfi-Bannerman et al. (ALPS trial) provided evidence that the administration of antenatal corticosteroids to women with a singleton pregnancy at risk of late-preterm birth decreases the risk of neonatal respiratory morbidity [5]. Based on these findings, the Society for Maternal-Fetal Medicine and the American College of Obstetricians and Gynecologists recommend that women at high risk of delivery during the late-preterm period should

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receive a course of betamethasone [6, 7]. Still, it should be emphasized that there is an ongoing debate on whether routine administration of antenatal corticosteroids during the late-preterm period is justified given the potential risks that have been associated with antenatal corticosteroids [8–11]. Crowther et al., suggested that the risk–benefit ratio depends in part on whether the findings of the ALPS trial can be generalized to the wider population of women at risk for late-preterm birth, as women at the highest risk of late preterm birth, such as those with twin gestations, were excluded from the ALPS trial [12].

Twin infants face an approximately 50% risk of late preterm birth [2, 13] and account for approximately one-third of infants born at $34^{0/7}$–$35^{6/7}$ weeks [14]. Thus, the question of whether the beneficial effects of antenatal corticosteroids observed in late-preterm singletons can be extrapolated to late preterm twins is of major importance. The answer to this question depends, in part, on whether the risk of respiratory morbidity among late preterm twin infants is similar to that observed in late-preterm singletons. However, while much has been published on the risks associated with late-prematurity in singletons [1, 3, 15–19], similar data on the risks of late-preterm twins are limited and conflicting [13, 14, 20–23]. Furthermore, the interpretation of available studies is limited by small sample size and by differences in the definition of respiratory morbidity. To overcome these limitations, we recently addressed this question by comparing the risk of respiratory morbidity between late preterm singletons and late preterm twin infants [24]. In that study, we used the same composite respiratory outcomes that were used in the ALPS trial [5] to facilitate comparison of the respiratory outcomes of late preterm twins and late-preterm singletons in a context that is relevant to the potential role of antenatal corticosteroids in late preterm twins. Although the rate of respiratory morbidity was similar between late preterm singletons and late preterm twins (7.4% and 8.3%, respectively, $p = 0.5$), it was considerably lower than the rate observed by Gyamfi-Bannerman et al., in the ALPS trial in either the placebo or betamethasone groups (14.4% and 11.6%, respectively), which may call into question the risk–benefit ratio of antenatal corticosteroids in this population. However, our study was limited by its retrospective design, size of the twins group and by the fact that it was conducted in a single tertiary referral center which questions the generalizability of its findings. Therefore, we thought that this question should be further addressed through larger prospective multicenter studies.

The aim of the current study was to assess the rate of respiratory morbidity, as defined in the ALPS trial [5], among late preterm twin infants, using a secondary analysis of prospectively collected data from a large international multicenter trial, and to compare that rate with previous studies that used the same definition of respiratory morbidity.

Materials and methods

Study population

We used a cohort study design based on data from a recent randomized controlled trial on mode of delivery in twin pregnancies [Twin Birth Study (TBS)] [25]. Women were enrolled in the TBS if they were between $32^{0/7}$ and $38^{6/7}$ weeks of gestation, the first twin was in the cephalic presentation, and both twins were alive with an estimated weight between 1500 and 4000 g. Exclusion criteria were monoamniotic twins, fetal reduction at 13 or more weeks of gestation, the presence of a lethal fetal anomaly and contraindication to labor or vaginal birth (e.g., fetal compromise, second twin substantially larger than the first twin, fetal anomaly or condition that might cause mechanical problems at delivery, and previous vertical uterine incision or more than one previous low-segment cesarean delivery). Participants were randomly assigned to planned cesarean section or planned vaginal birth. Data were abstracted from the medical records at participating centers by trained study staff and were recorded, after delivery, on standardized data-collection forms. Elective delivery by means of either cesarean delivery (for women in the planned-cesarean-delivery group) or labor induction (for women in the planned-vaginal-birth group) was planned between 37 weeks 5 days and 38 weeks 6 days of gestation. Overall the study included 2804 women who were recruited from 106 centers in 25 countries, of whom 2784 (1392 in the planned cesarean delivery group and 1392 in the planned vaginal delivery group) were included in the final analysis. The TBS and all secondary analyses were approved by the Research Ethics Board at the Sunnybrook Health Sciences Centre.

In the current study, we limited the analysis to women who gave birth during the late preterm period, defined as $34^{0/7}$–$36^{6/7}$ weeks of gestation.

Data collection

Data were abstracted from the TBS database and included the following information: maternal demographics and obstetrical history, chorionicity, gestational age at the time of randomization, gestational age at birth, presentations of both twins at the time of birth, birth weight, and fetal sex.

Outcomes

To facilitate the interpretation of neonatal respiratory morbidity in a context that is relevant to the potential role of antenatal corticosteroids in this group of late-preterm twin infants, we chose to use the same primary outcomes that

were used in the ALPS trial [5]. Thus, the primary outcome was a composite respiratory morbidity which was defined as need for respiratory support within 72 h after birth and consisted of one or more of the following: (1) use of continuous positive airway pressure (CPAP) or high-flow nasal cannula (> 1 L/min) for at least two consecutive hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, (3) extracorporeal membrane oxygenation (ECMO), (4) mechanical ventilation, or (5) stillbirth and neonatal death within 72 h after delivery. Severe respiratory morbidity was defined as one or more of the following: (1) need for respiratory support in the form of CPAP or high-flow nasal cannula for at least 12 continuous hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth or neonatal death within 72 h after delivery.

Bronchopulmonary dysplasia (BPD) was defined as the requirement for oxygen at postmenstrual age of 36 weeks or at the time of transfer to a Level II facility [26]. Severe neurological injury was defined as grade 3 or 4 intraventricular hemorrhage according to the criteria of Papile et al. [27] or periventricular leukomalacia, diagnosed by cranial ultrasound or magnetic resonance imaging. Necrotizing enterocolitis (NEC) was defined according to Bell's criteria [28].

Data analysis

Baseline characteristics and neonatal outcomes were stratified by gestational week at birth (34 [$34^{0/7}$–$34^{6/7}$], 35 [$35^{0/7}$–$35^{6/7}$] or 36 [$36^{0/7}$–$36^{6/7}$] weeks) and compared using one way analysis of variance (ANOVA) and Chi-square test for continuous and categorical variables, respectively. To test that neonatal respiratory morbidity is indeed attributed to late-prematurity rather than to the confounding effect of antepartum and intrapartum complications which may result in late-prematurity and can affect neonatal outcomes irrespective of gestational age, we repeated the analysis in the subgroup of 'low-risk' pregnancies after excluding pregnancies complicated by any of the following conditions: gestational or preexisting diabetes, placental abruption, chorioamnionitis, umbilical artery pH < 7.0, intrauterine fetal death or selective reduction of one or both fetuses, major congenital anomalies, or birth weight below 3rd percentile. Furthermore, we used multivariable logistic regression analysis to assess the association of gestational week at birth with respiratory morbidity while adjusting for potential confounding factors including: exposure to antenatal corticosteroids earlier in pregnancy, mode of delivery, twin order, preterm premature rupture of membranes for > 48 h, and chorionicity. These models were fitted with generalized estimating equations (GEE) to account for the correlation within twin pairs.

The rates of the composite respiratory outcomes observed in the current study were compared with corresponding rates previously reported by Gyamfi-Bannerman et al., in the ALPS trial among late preterm singletons exposed to betamethasone or placebo [5], as well as with the rates we previously reported among late preterm twins and singletons in our single-center cohort [24]. We calculated the theoretical absolute risk reduction (ARR) that could be achieved by betamethasone, assuming its effect in late-preterm twins would be identical to that observed in the ALPS trial in late-preterm singletons (relative risk of 0.80 for respiratory morbidity and relative risk of 0.67 for severe respiratory morbidity). This assumption is based on our recent findings that the effects of antenatal corticosteroids before 34 weeks of gestation are similar in twin and singleton pregnancies [29]. We calculated 95% confidence intervals for the ARR based on the method of Wald [30]. We finally calculated the corresponding theoretical number of women giving birth during the late preterm period needed to be treated with betamethasone to prevent a single case of respiratory morbidity and severe respiratory morbidity (NNT). Data were analyzed using the SAS statistical software version 9.4. Significance was set at a two-sided P value < 0.05.

Results

Characteristics of study groups

Of the original cohort of 2784 women, 1163 (41.8%) women gave birth during the late preterm period and were included in the current analysis. The characteristics of the study group by gestational week at birth are presented in Table 1. The three group differed in the rate of preterm premature rupture of membranes for > 48 h and the rate of prior exposure to antenatal corticosteroids earlier in pregnancy (which were highest among women who gave birth at $34^{0/7}$–$34^{6/7}$ weeks), and in the rate of induction of labor (which was highest among women who gave birth at $36^{0/7}$–$36^{6/7}$ weeks). The rest of the characteristics did not differ between the three gestational week groups (Table 1).

Neonatal outcomes

The overall unadjusted rates of neonatal respiratory morbidity and severe respiratory morbidity among late-preterm twins were 16.5% and 8.9%, respectively (Table 2). The rates differed significantly by gestational week at birth, being highest at $34^{0/7}$–$34^{6/7}$ weeks (31.9% and 17.2%, respectively) and lowest at $36^{0/7}$–$36^{6/7}$ weeks (9.5% and 4.6%, respectively). These findings persisted in the adjusted analysis: compared with infants born at $36^{0/7}$–$36^{6/7}$ weeks, those born at $34^{0/7}$–$34^{6/7}$ and $35^{0/7}$–$35^{6/7}$

Table 1 Demographic and obstetrical characteristics by gestational week at birth

Characteristic	Overall cohort ($N=1163$)[a]	$34^{0/7}$–$34^{6/7}$ weeks ($n=217$)[a]	$35^{0/7}$–$35^{6/7}$ weeks ($n=350$)[a]	$36^{0/7}$–$36^{6/7}$ weeks ($n=596$)[a]	*p* value
Maternal age (years)	29.1 ± 6.2	29.1 ± 6.6	28.9 ± 5.8	29.3 ± 6.3	0.707
Maternal age ≥ 35 years	217 (18.7%)	45 (20.7%)	52 (14.9%)	120 (20.1%)	0.091
Nulliparity	437 (37.6%)	91 (41.9%)	135 (38.6%)	211 (35.4%)	0.212
Monochorionic twins	319 (27.4%)	64 (29.5%)	99 (28.3%)	156 (26.2%)	0.581
pPROM for > 48 h	27 (2.3%)	11 (5.1%)	14 (4.0%)	2 (0.3%)	**< 0.001**
Antenatal corticosteroids	189 (16.3%)	49 (22.6%)	58 (16.6%)	82 (13.8%)	**0.010**
Induction of labor	115 (9.9%)	11 (5.1%)	26 (7. 5%)	78 (13.1%)	**0.001**
Cesarean delivery (Twin A)	751 (64.6%)	141 (65.0%)	221 (63.1%)	389 (65.7%)	0.797

Data are presented as mean ± SD or *n* (%)

Significant *p* values are emphasized in bold font

pPROM preterm premature rupture of membranes

[a]*N* refers to number of mothers (pregnancies)

Table 2 Neonatal respiratory morbidity

Outcome	Overall cohort ($N=2324$)[a]	$34^{0/7}$–$34^{6/7}$ weeks ($n=434$)[a]	$35^{0/7}$–$35^{6/7}$ weeks ($n=700$)[a]	$36^{0/7}$–$36^{6/7}$ weeks ($n=1190$)[a]	*p* value
Respiratory morbidity[b]	382 (16.5%)	138 (31.9%)	131 (18.8%)	113 (9.5%)	**< 0.001**
CPAP or high-flow nasal cannula for ≥ 2 continuous hrs	159 (6.9%)	53 (12.3%)	56 (8.1%)	50 (4.2%)	**< 0.001**
Fraction of inspired oxygen of ≥ 0.30 for ≥ 4 continuous hrs	311 (13.5%)	119 (27.7%)	104 (15.0%)	88 (7.5%)	**< 0.001**
ECMO	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Mechanical ventilation	59 (2.5%)	22 (5.1%)	14 (2.0%)	23 (1.9%)	**0.023**
Stillbirth or neonatal death ≤ 72 h after birth	11 (0.5%)	2 (0.5%)	4 (0.6%)	5 (0.4%)	0.880
Severe respiratory morbidity[c]	206 (8.9%)	74 (17.2%)	78 (11.3%)	54 (4.6%)	**< 0.001**
CPAP or high-flow nasal canula for ≥ 12 continuous hrs	122 (5.3%)	44 (10.2%)	42 (6.1%)	36 (3.1%)	**< 0.001**
Fraction of inspired oxygen of ≥ 0.30 for ≥ 24 continuous hrs	132 (5.7%)	47 (10.9%)	52 (7.5%)	33 (2.8%)	**< 0.001**

Data are presented as *n* (%)

Significant *p* values are emphasized in bold font

CPAP continuous positive airway pressure, *ECMO* extracorporeal membrane oxygenation, *N/A* non-applicable

[a]*N* refers to number of infants

[b]Respiratory morbidity was defined as need for respiratory support within 72 h after birth and consists of one or more of the following:(1) the use of CPAP or high-flow nasal cannula (> 1 L/min for at least two consecutive hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth and neonatal death within 72 h after delivery

[c]Severe respiratory morbidity was defined as one or more of the following:(1) need for respiratory support in the form of CPAP or high-flow nasal cannula for at least 12 continuous hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth or neonatal death within 72 h after delivery

weeks had a more than fourfold and twofold increased odds for respiratory morbidity, respectively (Table 3). Exposure to antenatal corticosteroids earlier in pregnancy and mode of delivery were not associated with the risk of respiratory morbidity (Table 3). Furthermore, the rates of respiratory morbidity and severe respiratory morbidity remained similar even when the analysis was restricted to women with low-risk twin pregnancies (15.7% and 8.6%, respectively) (Table S1).

Secondary neonatal outcomes are presented in Table 4. Overall, 18.6% of infants required resuscitation at birth, 8.0% required a prolonged NICU admission (≥ 48 h), 6.3% were diagnosed with respiratory distress syndrome and 10.5% were diagnosed with transient tachypnea of the newborn. The rates of these complications were highest at $34^{0/7}$–$34^{6/7}$ weeks and decreased considerably with each additional gestational week at birth (Table 4). The rates of other respiratory, infectious and neurological

Table 3 The association of gestational week at birth and other characteristics with respiratory morbidity among late preterm twins—multivariable analysis

Variable	Risk of respiratory morbidity Adjusted OR (95%–CI)	
	Respiratory morbidity[a]	Severe respiratory morbidity[b]
Gestational week at birth		
$36^{0/7}$–$36^{6/7}$ weeks	Reference	Reference
$35^{0/7}$–$35^{6/7}$ weeks	2.12 (1.51–2.98)	2.67 (1.70–4.20)
$34^{0/7}$–$34^{6/7}$ weeks	4.30 (3.01–6.14)	4.37 (2.74–6.95)
Exposure to antenatal corticosteroids (vs. no exposure as reference)	1.00 (0.70–1.44)	0.94 (0.60–1.47)
Cesarean section (vs. vaginal birth as reference)	1.18 (0.88–1.59)	1.45 (0.98–2.14)

Values reflect the results of multivariable logistic regression analysis and are adjusted for the following covariates: exposure to antenatal corticosteroids earlier in pregnancy, mode of delivery (cesarean vs. vaginal birth), twin order (first vs. second), preterm premature rupture of membranes for > 48 h, and chorionicity (dichorionic vs. monochorionic). Models were fitted with generalized estimating equations (GEE) to account for the correlation within a twin pairs, and were adjusted for the variables listed in the table. Significant associations are emphasized in bold font

OR odds ratio, *CI* confidence interval, *pPROM* preterm premature rupture of membranes

[a]Respiratory morbidity was defined as need for respiratory support within 72 h after birth and consists of one or more of the following: (1) the use of CPAP or high-flow nasal cannula (> 1 L/min) for at least two consecutive hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth and neonatal death within 72 h after delivery

[b]Severe respiratory morbidity was defined as one or more of the following: (1) need for respiratory support in the form of CPAP or high-flow nasal cannula for at least 12 continuous hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth or neonatal death within 72 h after delivery

Table 4 Secondary neonatal outcomes

Outcome	Overall cohort ($N = 2324$)[a]	$34^{0/7}$–$34^{6/7}$ weeks ($n = 434$)[a]	$35^{0/7}$–$35^{6/7}$ weeks ($n = 700$)[a]	$36^{0/7}$–$36^{6/7}$ weeks ($n = 1190$)[a]	*p* value
Male fetal sex	1167 (50.2%)	236 (54.4%)	337 (48.1%)	594 (49.9%)	0.119
Birth weight (g)	2391 ± 376	2136 ± 348	2340 ± 335	2514 ± 354	**< 0.001**
Birth weight < 10th percentile[†]	482 (20.7%)	73 (16.8%)	120 (17.1%)	289 (24.3%)	**< 0.001**
5 min Apgar < 7	45 (2.0%)	7 (1.6%)	15 (2.2%)	23 (2.0%)	0.805
Need for resuscitation at birth	431 (18.6%)	118 (27.3%)	146 (21.0%)	167 (14.1%)	**< 0.001**
NICU admission ≥ 48 h	184 (8.0%)	71 (16.5%)	64 (9.2%)	49 (4.2%)	**< 0.001**
Length of stay in NICU (h)	146 ± 155	178 ± 175	127 ± 127	123 ± 150	0.090
Respiratory distress syndrome	146 (6.3%)	52 (12.1%)	56 (8.1%)	38 (3.2%)	**< 0.001**
Transient tachypnea of the newborn	243 (10.5%)	79 (19.3%)	81 (11.4%)	83 (6.9%)	**< 0.001**
Use of surfactant	20 (0.9%)	5 (1.2%)	7 (1.0%)	8 (0.7%)	0.669
Pneumothorax	4 (0.2%)	0 (0.0%)	1 (0.1%)	3 (0.3%)	0.823
Bronchopulmonary dysplasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Neonatal sepsis	19 (0.8%)	7 (1.6%)	3 (0.4%)	9 (0.8%)	0.172
Severe neurological injury[‡]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A
Necrotizing enterocolitis (stage 2 or 3)	3 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)	0.809
Neonatal death ≤ 28 days after birth	19 (0.8%)	4 (0.9%)	7 (1.0%)	8 (0.7%)	0.714

Data are presented as mean ± SD or *n* (%)

Significant *p* values are emphasized in bold font s

NICU neonatal intensive care unit

[a]*N* refers to number of infants

[b]Based on sex-specific Canadian birth weight reference [33]

[c]Defined as grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia

complications, as well as of necrotizing enterocolitis and neonatal death were very low (< 1%) and did not differ between the gestational week at birth groups (Table 4).

Comparison of respiratory morbidity rate with previous reports

We compared the rates of the respiratory morbidity and severe respiratory morbidity composite variables observed in the current study among late-preterm twins ($n = 2324$) with the corresponding rates of these variables among late preterm singleton exposed to betamethasone ($n = 1400$) or placebo ($n = 1427$) in the ALPS trial [5]. and among late preterm singletons ($n = 922$) and late preterm twins ($n = 721$) in our previous single-center cohort study (Salem et al., 2017) [24] (Table 5). In contrast to the rates in the study of Salem et al. which were significantly lower than the rates reported in ALPS trial, the rates of respiratory morbidity in the current study were higher, and were similar to the rates reported in the ALPS trial for the placebo group (16.5% vs. 14.4%, $p = 0.103$) (Table 5). The theoretical number of women needed to be treated with betamethasone to prevent a single case of respiratory morbidity (assuming the effect of betamethasone in twins would be similar to that observed in the ALPS trial in singletons) in the current study was similar to that reported in the ALPS trial (NNT 31 vs. 34) (Table 5). With regard to severe respiratory morbidity, the rate of severe neonatal morbidity in the current study was lower than that reported in the ALPS trial for the placebo group (8.9% vs. 12.1%, $p = 0.002$), but was higher than that observed by Salem et al.

Discussion

Main findings

The aim of the current study was to assess the risk of respiratory morbidity in a large, prospective, international multi-center cohort of late-preterm twin infants, and to compare it with previous studies that used the same outcome measures. Our main findings were as follows: (1) late prematurity is associated with a considerable risk of neonatal respiratory morbidity in twins; this risk is highly dependent on gestational week at birth, peaking at 34 weeks and dropping considerably with each additional week of gestation; (2) the risk of respiratory morbidity observed in the current study among late-preterm twins is similar to that observed by Gyamfi-Bannerman et al., in a randomized controlled trial on betamethasone in late preterm singletons.

Interpretation of the results in the context of previous observations

Almost half of twin infants are born during the late preterm period [2, 13]. Therefore, there is an urgent need to determine whether the recent findings regarding a beneficial effect of antenatal corticosteroids in late preterm singletons [5] can be extrapolated to twin pregnancies. Overall, we believe that such extrapolation is reasonable given our recent findings that the beneficial effects of antenatal corticosteroids, when administered before 34 weeks of gestation, are similar in twin and singleton pregnancies [29]. However, one important factor that will determine the risk–benefit of such a practice (i.e., administration of antenatal corticosteroids to women with twins at risk of preterm birth during the late-preterm period), and was the focus of the current study, is whether the magnitude of risk of respiratory morbidity among late preterm twins is similar to that observed in late-preterm singletons in the ALPS trial.

Data on the outcomes of late-preterm twins compared with late-preterm singletons are limited and conflicting [14, 20–23, 31, 32]. Furthermore, interpretation of available studies is limited by small sample size of the late-preterm twins groups (124–363 [21, 23, 24]), by lack of focus on the late preterm period [20–22, 31], by differences in the definition of respiratory morbidity, and by lack of adjustment for factors such as exposure to antenatal corticosteroids earlier in gestation. In a recent study from our center [24], we found that although the rate of respiratory morbidity was similar between late preterm singletons and late preterm twins, it was considerably lower than the rate observed by Gyamfi-Bannerman et al., in the ALPS trial. This discrepancy may be attributed to the fact that respiratory morbidity in that study was ascertained retrospectively, and that the infants included in that study were managed in a single leading tertiary referral center, limiting external validity of these findings. In the current study, we have tried to address some of these limitations. Using a large, international multicenter prospective cohort of late-preterm twins, we found that the rate of respiratory morbidity (defined using the same composite outcome that was used in the ALPS trial and that was found to be reduced by administration of antenatal corticosteroids) among late preterm twins is similar to that reported by Gyamfi-Bannerman et al., among late-preterm singletons. Following the assumption made above that the biological effect of antenatal corticosteroids in late-preterm twins would be similar to that observed in late-preterm singletons, we found that the number of women with twins giving birth during the late-preterm period needed to be treated with betamethasone to prevent a single case of respiratory morbidity (NNT) would be 31, which is acceptable and is very similar to the NNT of 35 reported in the ALPS trial for late preterm singletons.

Table 5 Comparison of the rate of respiratory morbidity among late preterm infants with previous studies

Study	Population	*N*	Respiratory morbidity[a]					Severe respiratory morbidity[b]				
			Events	Rate (%)	*p* value	ARR(%) (95%–CI)[c]	NNT (95%–CI)	Events	Rate (%)	*p* value	ARR(%) (95%–CI)[c]	NNT (95%–CI)
ALPS trial, Gyamfi-Bannerman et al. (Placebo) [1]	Singletons	1400	202	14.4%	Ref	2.9 (0.4–5.4)	34 (19–250)	169	12.1%	Ref	4.0 (1.8–6.2)	25 (16–56)
ALPS trial, Gyamfi-Bannerman et al. (Betamethasone) [1]	Singletons	1427	165	11.6%	**0.023**	N/A	N/A	115	8.1%	**< 0.001**	N/A	N/A
Salem et al. [2]	Singletons	922	68	7.4%	**< 0.001**	1.5 (− 0.8 to 3.8)	68 (26–125)	55	6.0%	**< 0.001**	2.0 (0.0–4.0)	51 (25–1000)
Salem et al. [2]	Twins	721	60	8.3%	**< 0.001**	1.7 (− 1.1 to 4.4)	60 (23–91)	49	6.8%	**< 0.001**	2.2 (-0.1 to 4.6)	45 (22–1000)
Current study	Twins	2324	382	16.5%	0.103	3.3 (1.2–5.2)	31 (19–83)	206	8.9%	**0.002**	2.9 (1.5–4.6)	34 (22–67)

ALPS antenatal late preterm steroids, *ARR* absolute risk reduction, *NNT* number needed to treat, *N/A* not applicable

Significant *p* values are emphasized in bold font

[a]Respiratory morbidity was defined as need for respiratory support within 72 h after birth and consists of one or more of the following: (1) the use of CPAP or high-flow nasal cannula (> 1 L/min) for at least two consecutive hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth and neonatal death within 72 h after delivery

[b]Severe respiratory morbidity was defined as one or more of the following: (1) need for respiratory support in the form of CPAP or high-flow nasal cannula for at least 12 continuous hours, (2) supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, (3) ECMO, (4) mechanical ventilation, or (5) stillbirth or neonatal death within 72 h after delivery

[c]The theoretical absolute risk reduction (assuming betamethasone would have a similar effect in late-preterm twins to that observed in late preterm singletons) was calculated based on the effect of betamethasone in the study of Gyamfi-Bannerman et al.[1]: relative risk of 0.80 for respiratory morbidity and 0.67 for severe respiratory morbidity

Strengths and limitations

The main limitation of the current study is the fact that it is based on a secondary analysis of data from a trial that was not focused on neonatal respiratory morbidity during the late preterm period. Another limitation is the lack of a control group of late preterm singletons, so that direct comparison between late preterm twins and late preterm singletons within the current study was not possible.

The main strengths of the current study are the large sample size, the availability of detailed prospectively collected neonatal data that allowed us to replicate the same composite variables used in the ALPS trial, and the multi center design which contributes to the generalizability and external validity of the findings of the current study.

Conclusion

We found that the risk of respiratory morbidity among late preterm twins is similar to that observed among late preterm singletons. This finding, along with previous evidence that the effect of antenatal corticosteroids in twins is expected to be similar to that observed in singletons [29], suggest that the risk–benefit ratio of betamethasone with regard to neonatal respiratory morbidity in women with twins at risk of late preterm birth may be similar to that observed in singletons. These findings are of major importance considering the fact that twins account for approximately one-third of infants born at $34^{0/7}$–$35^{6/7}$ weeks and since a large randomized controlled trial on antenatal corticosteroids in late preterm twin, similar to that performed by Gyamfi-Bannerman et al., in singletons, is unlikely to be conducted in the near future. It should be emphasized that there is an ongoing debate on whether routine administration of antenatal corticosteroids to women at risk of late preterm birth (with either singleton or twin pregnancy) is justified. This debate is related to what is considered by some to be an only modest beneficial effect of antenatal corticosteroids in the late-preterm period in the context of recent reports on potential long-term risks associated with exposure to antenatal corticosteroids among term infants [8–11]. Still, the findings of the current study suggest that care providers and medical centers that currently administer betamethasone to women with a singleton pregnancy during the late-preterm period, may consider extending this practice to women with twin gestations as well.

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Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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