ORIGINAL ARTICLE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

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ABSTRACT

BACKGROUND

Infants who are born at 34 to 36 weeks of gestation (late preterm) are at greater risk for adverse respiratory and other outcomes than those born at 37 weeks of gestation or later. It is not known whether betamethasone administered to women at risk for late preterm delivery decreases the risks of neonatal morbidities.

METHODS

We conducted a multicenter, randomized trial involving women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation who were at high risk for delivery during the late preterm period (up to 36 weeks 6 days). The participants were assigned to receive two injections of betamethasone or matching placebo 24 hours apart. The primary outcome was a neonatal composite of treatment in the first 72 hours (the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 hours, extracorporeal membrane oxygenation, or mechanical ventilation) or stillbirth or neonatal death within 72 hours after delivery.

RESULTS

The primary outcome occurred in 165 of 1427 infants (11.6%) in the betamethasone group and 202 of 1400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval [CI], 0.66 to 0.97; P=0.02). Severe respiratory complications, transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia also occurred significantly less frequently in the betamethasone group. There were no significant between-group differences in the incidence of chorioamnionitis or neonatal sepsis. Neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001).

CONCLUSIONS

Administration of betamethasone to women at risk for late preterm delivery significantly reduced the rate of neonatal respiratory complications. (Funded by the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ClinicalTrials.gov number, NCT01222247.)

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*A complete list of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units Network is provided in the Supplementary Appendix, available at NEJM.org.

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Antenatal glucocorticoids are widely used in obstetrics for pregnancies at risk for early preterm delivery. Their use increased especially after a consensus conference held by the National Institutes of Health in 1994, which concluded that there was strong evidence that glucocorticoids reduce adverse neonatal outcomes, including death, the respiratory distress syndrome, and other complications, when administered to women who are likely to deliver before 34 weeks of gestation.[1-3] The recommendation was not extended to women at risk for preterm delivery after 34 weeks because of both a lack of data[4,5] and the belief that at a threshold of 34 to 35 weeks of gestation nearly all infants thrive, with survival at this gestational age being within 1% of survival at term.[6] However, it is now clear that infants who are born during the late preterm period (34 weeks 0 days to 36 weeks 6 days) have more neonatal and childhood complications than do newborns who are born at term (37 weeks or later).[7-9] Because of this, a workshop in 2005 recommended redirecting research to evaluate infants who are born between 34 and 36 weeks of gestation, particularly to answer the question of whether antenatal glucocorticoids are beneficial in this population.[10] Currently, 8% of all deliveries occur in the late preterm period.[11] Thus, the potential public health and economic effects of decreasing the rate of complications associated with late prematurity by the administration of antenatal glucocorticoids are considerable. We designed a randomized trial to assess whether the administration of betamethasone to women who are likely to deliver in the late preterm period would decrease respiratory and other neonatal complications.

Methods

Study Oversight

We conducted the trial at 17 university-based clinical centers participating in the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board at each center. Written informed consent was obtained from all participants before randomization. The first, second, and fifth authors take responsibility for the accuracy and completeness of the reporting and the fidelity of the report to the study protocol.

Screening and Recruitment

Women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation and a high probability of delivery in the late preterm period (which extends to 36 weeks 6 days) were eligible for enrollment. High probability of delivery was defined as either preterm labor with intact membranes and at least 3 cm dilation or 75% cervical effacement, or spontaneous rupture of the membranes. If neither of these criteria applied, a high probability was defined as expected preterm delivery for any other indication either through induction or cesarean section between 24 hours and 7 days after the planned randomization, as determined by the obstetrical provider.

A woman was ineligible if she had received antenatal glucocorticoids previously during the pregnancy or if she was expected to deliver in less than 12 hours for any reason, including ruptured membranes in the presence of more than six contractions per hour or cervical dilation of 3 cm or more unless oxytocin was withheld for at least 12 hours (although other induction agents were allowed), chorioamnionitis, cervical dilation of 8 cm or more, or evidence of nonreassuring fetal status requiring immediate delivery. Gestational age was determined by means of a method standardized across sites. Exclusion criteria included the lack of gestational-dating results on ultrasonography before 32 weeks for a woman with a known date of the last menstrual period or before 24 weeks of gestation for those with an unknown date of the last menstrual period. Full eligibility criteria are provided in the Supplementary Appendix, available at NEJM.org.

Randomization and Treatment

Eligible and consenting women were randomly assigned in a 1:1 ratio to a course of two intramuscular injections containing either 12 mg of betamethasone (equal parts betamethasone sodium phosphate and betamethasone acetate) or matching placebo administered 24 hours apart. The randomization sequence was prepared by the independent data-coordinating center with the use of the simple urn method,[12] with stratification according to clinical site and gestational-age category (34 to 35 weeks vs. 36 weeks). Each

participant's supply of study medication was packaged according to this sequence. Neither the participants nor the investigators were aware of study-group assignments. During the trial, we changed the company that was in charge of manufacturing the placebo and packaging the study medication. This resulted in suspension of recruitment until a new company was identified. (Additional details are provided in the Supplementary Appendix.)

After administration of the study medication, the women were treated clinically according to local practice, including discharge home if delivery did not occur and the patient's condition was considered to be stable. For those enrolled because of an indication for preterm delivery, labor inductions were expected to start by 36 weeks 5 days, and cesarean deliveries were to be scheduled by 36 weeks 6 days and not before 24 hours after randomization. Trained and certified research staff members abstracted information from maternal and neonatal charts, including demographic information and outcome data, along with medical, obstetrical, and social history. Follow-up was performed at 28 days after birth for all infants who were receiving oxygen at the time of discharge to determine whether there was a continuing need for oxygen supplementation.

STUDY OUTCOMES

The primary outcome was a composite end point describing the need for respiratory support within 72 hours after birth and consisting of one or more of the following: the use of continuous positive airway pressure (CPAP) or high-flow nasal cannula for at least 2 consecutive hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 continuous hours, extracorporeal membrane oxygenation (ECMO), or mechanical ventilation. A high flow of air or blended air and oxygen was defined as more than 1 liter per minute. Stillbirth and neonatal death within 72 hours after delivery were also included in the composite outcome as competing events.

Prespecified subgroup analyses for the primary outcome and severe respiratory complications were a comparison of a gestational age of 34 to 35 weeks versus 36 weeks at randomization, the indication for trial entry (preterm labor, spontaneous membrane rupture, or obstetrical or medical indication), a planned cesarean delivery versus a planned attempt at vaginal delivery at trial entry, infant sex, and race or ethnic group.

Neonatal secondary outcomes included the following: severe respiratory complications (a composite outcome of CPAP or high-flow nasal cannula for at least 12 continuous hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least at least 24 continuous hours, ECMO or mechanical ventilation, stillbirth, or neonatal death within 72 hours after delivery), the respiratory distress syndrome, transient tachypnea of the newborn, apnea, bronchopulmonary dysplasia, surfactant administration, need for resuscitation at birth, hypoglycemia, feeding difficulty, hypothermia, necrotizing enterocolitis, intraventricular hemorrhage Papile grade 3 or 4,[13] neonatal sepsis, pneumonia, and death before discharge. The respiratory distress syndrome was defined as the presence of clinical signs of respiratory distress (tachypnea, retractions, flaring, grunting, or cyanosis), with a requirement for supplemental oxygen with a fraction of inspired oxygen of more than 0.21 and a chest radiograph showing hypoaeration and reticulogranular infiltrates. Transient tachypnea of the newborn was diagnosed when tachypnea occurred in the absence of chest radiography or with a radiograph that was normal or showed signs of increased perihilar interstitial markings and resolved within 72 hours. Bronchopulmonary dysplasia was defined as a requirement for supplemental oxygen with a fraction of inspired oxygen of more than 0.21 for the first 28 days of life. Hypoglycemia was defined as a glucose level of less than 40 mg per deciliter (2.2 mmol per liter) at any time.

Two composite outcomes were also prespecified: one consisting of the respiratory distress syndrome, transient tachypnea of the newborn, or apnea; and the other, the respiratory distress syndrome, intraventricular hemorrhage, or necrotizing enterocolitis. Maternal secondary outcomes included chorioamnionitis, endometritis, delivery before completion of the course of glucocorticoids, and length of hospitalization. Definitions of all secondary outcomes are provided in the Supplementary Appendix.

Charts of all infants who were admitted to special care nurseries were centrally reviewed by a subgroup of the investigators and nurse coordinators to verify the respiratory outcomes. Discrepancies among the reviewers, or between local research staff members and reviewers, were ad-

judicated by an independent neonatal consultant who also reviewed all potential cases of bronchopulmonary dysplasia. All the reviewers were unaware of study-group assignments.

STATISTICAL ANALYSIS

We estimated the expected rate of the primary outcome in the placebo group on the basis of the results of a pilot study of infants born at 34 to 36 weeks of gestation after adjustment to account for women at risk for late preterm delivery who deliver at term. We estimated that 2800 women would provide a power of at least 85% to detect a relative decrease of 33% in the rate of the primary outcome, from 9.5% in the placebo group to 6.3% in the betamethasone group, with a two-sided type I error rate of 5%. Details regarding the power analysis are provided in the Supplementary Appendix.

Analyses were performed according to the intention-to-treat principle. We compared continuous variables using the Wilcoxon test and categorical variables using chi-square and Fisher's exact tests. An independent data and safety monitoring committee monitored the trial. We used a group sequential method to control the type I error with the Lan–DeMets characterization of the O'Brien–Fleming boundary.[14] Two interim analyses were performed; in the final analysis of the primary outcome, a two-tailed P value of less than 0.048 was considered to indicate statistical significance. Since the adjustment is minimal, we report the 95% confidence interval for the relative risk. For all secondary outcomes, a nominal P value of less than 0.05 was considered to indicate statistical significance, without adjustment for multiple comparisons; relative risks and 95% confidence intervals are reported. To determine whether there was a differential effect of betamethasone for the primary outcome and the composite outcome of severe respiratory complications within the prespecified subgroups, we performed the Breslow–Day interaction test in which a nominal P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

Recruitment began in October 2010 and concluded in February 2015. Of 24,133 women who underwent screening, 2831 eligible participants underwent randomization (with 1429 assigned to the betamethasone group and 1402 to the placebo group) (Fig. 1). The most common reason for exclusion was the expectation that delivery would occur within 24 hours, which was determined in 6203 of 19,587 women (31.7%) who did not meet the eligibility criteria. The betamethasone and placebo groups were similar at baseline except for maternal age (mean, 28.6 vs. 27.8 years; P=0.001) and the proportion of women of Hispanic ethnic background (28.3% vs. 32.0%, P=0.03) (Table 1).

COMPLIANCE AND SIDE EFFECTS

A total of 860 of 1429 women (60.2%) in the betamethasone group and 826 of 1402 (58.9%) in the placebo group received the prespecified two doses of study medication. Of the 1145 women who did not receive a second dose, 1083 (94.6%) delivered before 24 hours; 6 women did not receive any of the assigned study medication. (In the placebo group, 3 women who consented to participate in the trial subsequently declined the injection, 1 woman delivered after randomization but before the first dose, and 1 received open-label betamethasone. In the betamethasone group, 1 woman was in active labor with complete cervical dilation at the time of randomization.)

Adverse events that were reported after both injections were less common in the betamethasone group than in the placebo group (rate after first injection, 14.1% vs. 20.3%; P<0.001; rate after second injection, 5.5% vs. 9.5%; P<0.007). Almost all adverse events (95%) were local reactions at the injection site (Table S4 in the Supplementary Appendix).

NEONATAL OUTCOMES

Two women in each study group were lost to follow-up, so outcome information was available for 2827 neonates. There were no stillbirths or neonatal deaths within 72 hours. The rate of the primary outcome was lower in the betamethasone group than in the placebo group (11.6% vs. 14.4%; relative risk, 0.80; 95% confidence interval [CI], 0.66 to 0.97; P=0.02) (Table 2). We determined that 35 women (95% CI, 19 to 259) would need to be treated to prevent one case of the primary outcome. Results remained materially unchanged in post hoc analyses after adjustment for maternal age and Hispanic ethnic group and with the exclusion of infants (11 in the beta-

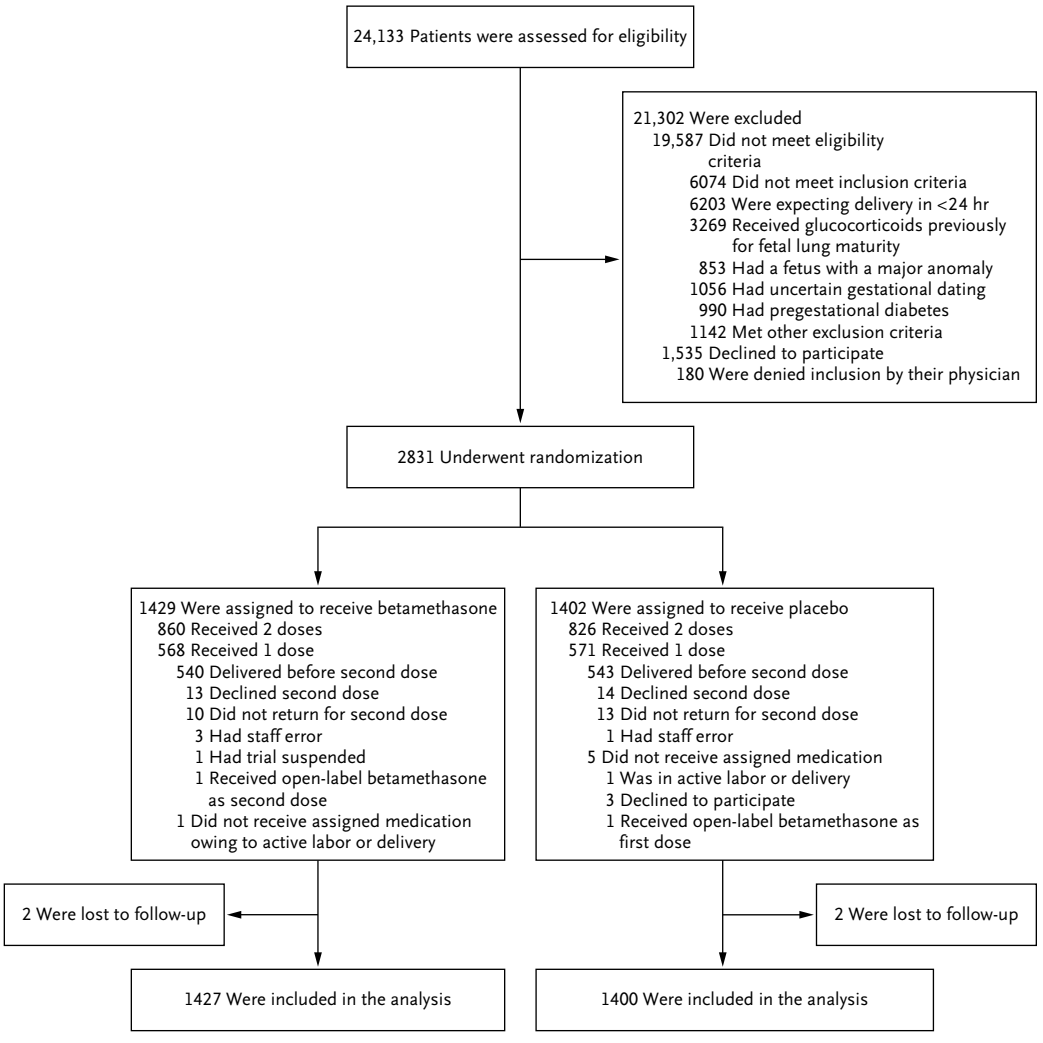

Figure 1. Screening, Enrollment, Randomization, and Follow-up.

methasone group and 21 in the placebo group) who had a major congenital anomaly that was not recognized until after delivery.

The rate of the composite outcome of severe respiratory complications was also significantly lower in the betamethasone group than in the placebo group (8.1% vs. 12.1%; relative risk, 0.67; 95% CI, 0.53 to 0.84; P<0.001). The number needed to treat to prevent one case was 25 (95% CI, 16 to 56). The rates of the respiratory distress syndrome, apnea, and pneumonia were similar in the two groups, but rates of several disorders were significantly lower in the betamethasone group than in the placebo group, including transient tachypnea of the newborn (6.7% vs. 9.9%), bronchopulmonary dysplasia (0.1% vs. 0.6%), and the composite of the respiratory distress syndrome, transient tachypnea of the newborn, or apnea (13.9% vs. 17.8%); there was also a significantly lower rate of resuscitation at birth (14.5% vs. 18.7%) and surfactant use (1.8% vs. 3.1%) (Table 2).

None of the subgroup interaction tests for the primary outcome were significant. There was one marginally significant interaction (P=0.05) between treatment group and planned delivery type for the secondary outcome of severe respiratory complications, with a significant reduction in the betamethasone group among those for whom cesarean delivery was planned at trial

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Betamethasone (N=1429)	Placebo (N=1402)
Indication for trial entry — no. (%)		
Preterm labor with intact membranes	400 (28.0)	392 (28.0)
Ruptured membranes	316 (22.1)	304 (21.7)
Expected delivery for gestational hypertension or preeclampsia	370 (25.9)	385 (27.5)
Expected delivery for fetal growth restriction	46 (3.2)	48 (3.4)
Expected delivery for oligohydramnios	50 (3.5)	42 (3.0)
Expected delivery for other indication	247 (17.3)	231 (16.5)
Gestational age at trial entry — no. (%)		
≤34 wk 6 days	369 (25.8)	399 (28.5)
35 wk 0 days to 35 wk 6 days	571 (40.0)	532 (37.9)
≥36 wk 0 days	489 (34.2)	471 (33.6)
Mean (±SD) maternal age — yr	28.6±6.3	27.8±6.1
Race or ethnic group — no. (%)†		
Black	376 (26.3)	381 (27.2)
White	828 (57.9)	800 (57.1)
Asian	57 (4.0)	39 (2.8)
Other, unknown, or more than one race	168 (11.8)	182 (13.0)
Hispanic	405 (28.3)	448 (32.0)
Nulliparous — no. (%)	457 (32.0)	448 (32.0)
Smoking during current pregnancy — no. (%)	204 (14.3)	186 (13.3)
Preeclampsia or gestational hypertension — no. (%)	433 (30.3)	440 (31.4)
Gestational diabetes — no. (%)	153 (10.7)	153 (10.9)
Major congenital anomaly in infant — no. (%)‡	11 (0.8)	21 (1.5)

* There were no significant differences between the two groups except for maternal age (P=0.001) and Hispanic ethnic group (P=0.03).
† Race or ethnic group was self-reported. Patients of any race could report Hispanic background.
‡ Although the presence of a major congenital anomaly was an exclusion criterion, these disorders were not discovered until birth.

entry but not among those planning to attempt a vaginal delivery (Tables S5 and S6 in the Supplementary Appendix).

Two infants (both in the betamethasone group) died before discharge: one death was due to septic shock and the other to a structural cardiac anomaly and arrhythmia. There were no significant between-group differences in the gestational age at delivery, the frequency of categorization as small for gestational age, length of hospital stay, or rate of neonatal sepsis, necrotizing enterocolitis, intraventricular hemorrhage, hyperbilirubinemia, hypothermia, or a composite of the respiratory distress syndrome, intraventricular hemorrhage, or necrotizing enterocolitis (Table 3). As compared with infants in the placebo group, infants in the betamethasone group were less likely to spend 3 or more days in the intensive or intermediate care nursery (P=0.03) and had a shorter time until the first feeding (P=0.004) but had a higher incidence of neonatal hypoglycemia (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001).

MATERNAL OUTCOMES

There were no significant between-group differences in the incidence of chorioamnionitis or endometritis. The rates of cesarean delivery, time to delivery, and length of stay were also similar in the two groups (Table 4).

Table 2. Neonatal Respiratory Outcomes.*

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value
	no. (%)			
Primary outcome†	165 (11.6)	202 (14.4)	0.80 (0.66–0.97)	0.02
CPAP or high-flow nasal cannula for ≥2 continuous hr	145 (10.2)	184 (13.1)	0.77 (0.63–0.95)	0.01
Fraction of inspired oxygen of ≥0.30 for ≥4 continuous hr	48 (3.4)	61 (4.4)	0.77 (0.53–1.12)	0.17
Mechanical ventilation	34 (2.4)	43 (3.1)	0.78 (0.50–1.21)	0.26
ECMO	0	0	NA	NA
Stillbirth or neonatal death ≤72 hr after birth	0	0	NA	NA
Severe respiratory complication‡	115 (8.1)	169 (12.1)	0.67 (0.53–0.84)	<0.001
CPAP or high-flow nasal cannula for ≥12 continuous hr	93 (6.5)	147 (10.5)	0.62 (0.48–0.80)	<0.001
Fraction of inspired oxygen of ≥0.30 for ≥24 continuous hr	20 (1.4)	34 (2.4)	0.58 (0.33–1.00)	0.05
Need for resuscitation at birth§	206 (14.5)	260 (18.7)	0.78 (0.66–0.92)	0.003
Respiratory distress syndrome	79 (5.5)	89 (6.4)	0.87 (0.65–1.17)	0.36
Transient tachypnea of the newborn	95 (6.7)	138 (9.9)	0.68 (0.53–0.87)	0.002
Apnea	33 (2.3)	37 (2.6)	0.88 (0.55–1.39)	0.57
Bronchopulmonary dysplasia	2 (0.1)	9 (0.6)	0.22 (0.02–0.92)¶	0.04
Pneumonia	6 (0.4)	13 (0.9)	0.45 (0.17–1.19)	0.10
Surfactant use	26 (1.8)	43 (3.1)	0.59 (0.37–0.96)	0.03
Composite of respiratory distress syndrome, transient tachypnea of the newborn, or apnea	198 (13.9)	249 (17.8)	0.78 (0.66–0.93)	0.004
Pulmonary air leak	5 (0.4)	6 (0.4)	0.82 (0.25–2.68)	0.74

* Two participants in each group were lost to follow-up for the analysis of neonatal respiratory outcomes. CI denotes confidence interval, CPAP continuous positive airway pressure, ECMO extracorporeal membrane oxygenation, and NA not applicable.

† The primary outcome was defined as any of the following occurrences within 72 hours after birth: CPAP or high-flow nasal cannula for at least 2 continuous hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 4 continuous hours, mechanical ventilation, stillbirth or neonatal death, or the need for ECMO.

‡ A severe respiratory complication was defined as any of the following occurrences within 72 hours after birth: CPAP or high-flow nasal cannula for at least 12 hours, supplemental oxygen with a fraction of inspired oxygen of 0.30 or more for at least 24 hours, mechanical ventilation, stillbirth or neonatal death, or the need for ECMO. Except for the duration of CPAP or high-flow nasal cannula and the duration of a fraction of inspired oxygen of 0.30 or more, the criteria for a severe respiratory complication overlap with those of the primary outcome.

§ The need for resuscitation at birth was evaluated in 1422 infants in the betamethasone group and 1390 in the placebo group.

¶ Exact confidence limits are provided for the difference between two binomial proportions.[15]

SERIOUS ADVERSE EVENTS

Serious maternal adverse events occurred in 10 women in the betamethasone group and 12 in the placebo group (Table S7 in the Supplementary Appendix). Apart from the neonatal deaths, only one serious neonatal adverse event occurred (a case of thrombocytopenia in the betamethasone group).

DISCUSSION

In this randomized, multicenter trial, we found that antenatal administration of betamethasone to women at risk for late preterm delivery decreased the need for substantial respiratory support during the first 72 hours after birth. Betamethasone administration also resulted in reduced rates of

Table 3. Other Secondary Neonatal Outcomes.*

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value
Neonatal death — no. (%)	2 (0.1)	0	NA	0.50
Mean (±SD) birth weight — g	2637±480	2654±484		0.32
Birth weight in <10th percentile — no. (%)	255 (17.9)	220 (15.7)	1.14 (0.96–1.34)	0.13
Gestational age at delivery — no. (%)				0.10
≤34 wk 6 days	193 (13.5)	213 (15.2)		
35 wk 0 days to 35 wk 6 days	394 (27.6)	386 (27.6)		
36 wk 0 days to 36 wk 6 days	609 (42.7)	568 (40.6)		
37 wk 0 days to 38 wk 6 days	202 (14.2)	185 (13.2)		
≥39 wk 0 days	29 (2.0)	48 (3.4)		
Necrotizing enterocolitis — no. (%)	0	1 (0.1)		
Proven neonatal sepsis — no. (%)	9 (0.6)	11 (0.8)	0.80 (0.33–1.93)	0.62
Grade 3–4 intraventricular hemorrhage — no. (%)	2 (0.1)	0		
Composite of respiratory distress syndrome, intraventricular hemorrhage, or necrotizing enterocolitis — no. (%)	81 (5.7)	90 (6.4)	0.88 (0.66–1.18)	0.40
Hypoglycemia — no. (%)†	343 (24.0)	210 (15.0)	1.60 (1.37–1.87)	<0.001
Median time until first feeding (IQR) — hr	5.5 (1.4–24.7)	9.9 (1.7–29.1)		0.004
Feeding difficulty — no. (%)	211 (14.8)	223 (15.9)	0.93 (0.78–1.10)	0.40
Hyperbilirubinemia — no. (%)	167 (11.7)	140 (10.0)	1.17 (0.95–1.40)	0.15
Hypothermia — no. (%)	132 (9.3)	112 (8.0)	1.16 (0.91–1.47)	0.24
Admission to intermediate care nursery or NICU — no. (%)				
Any duration	596 (41.8)	629 (44.9)	0.93 (0.85–1.01)	0.09
Duration ≥3 days	470 (32.9)	518 (37.0)	0.89 (0.80–0.98)	0.03
Median length of hospital stay (IQR) — days	7 (4–12)	8 (4–13)		0.20

* Two participants in each group were lost to follow-up for the analysis of other secondary neonatal outcomes. IQR denotes interquartile range, and NICU neonatal intensive care unit.
† Hypoglycemia was defined as a glucose level of less than 40 mg per deciliter (2.2 mmol per liter).

severe respiratory complications, transient tachypnea of the newborn, and bronchopulmonary dysplasia, along with reduced rates of surfactant use, resuscitation, and a prolonged stay in a special care nursery. These benefits were found despite the challenges in predicting the timing of delivery, which resulted in the administration of two doses of the study drugs to only 60% of participants.

Our findings are consistent with the results of the Antenatal Steroids for Term Elective Caesarean Section (ASTECS) trial, in which women were randomly assigned to receive either antenatal glucocorticoids or no glucocorticoids at the time of elective cesarean delivery at term. There was a significant reduction in the rate of admission to neonatal intensive care units for respiratory complications in the betamethasone group (relative risk, 0.46; 95% CI, 0.23 to 0.93).[16] Treatment with betamethasone among patients undergoing a scheduled cesarean at term has since become the standard of care in the United Kingdom. Two smaller randomized trials have specifically assessed the use of betamethasone in the late preterm period to prevent adverse neonatal respiratory outcomes.[17,18] However, these studies were inconclusive, since they were underpowered,[18] had substantial loss to follow-up,[17] and had exclusions after randomization.[18]

Table 4. Maternal Outcomes.*

Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value
Chorioamnionitis — no. (%)	20 (1.4)	32 (2.3)	0.61 (0.35–1.07)	0.08
Postpartum endometritis — no. (%)	16 (1.1)	16 (1.1)	0.98 (0.49–1.95)	0.96
Cesarean delivery — no. (%)	454 (31.8)	431 (30.8)	1.03 (0.93–1.15)	0.56
Median interval from randomization to delivery (IQR) — hr	33.0 (15.2–111.6)	30.6 (14.6–111.0)		0.57
Median length of hospital stay (IQR) — days	3 (3–5)	3 (3–5)		0.11

* Two participants in each group were lost to follow-up for the analysis of maternal outcomes.

The administration of betamethasone did not significantly affect rates of peripartum maternal or neonatal infection but increased the rate of neonatal hypoglycemia, a common late preterm neonatal complication.[19] We did not collect data on blood glucose levels over time. However, there were no reported adverse events related to hypoglycemia, which was not associated with an increased length of hospital stay. Infants with hypoglycemia were discharged on average 2 days earlier than those without hypoglycemia, which suggests that the condition was self-limiting. Few trials of antenatal glucocorticoids have included information on neonatal hypoglycemia.[4] However, the original trial of antenatal glucocorticoids showed no significant between-group difference in the rates of neonatal hypoglycemia.[20] Nevertheless, our data support monitoring neonatal blood glucose after betamethasone exposure in the late preterm period.

It is possible that the reduction in the rate of bronchopulmonary dysplasia with betamethasone therapy could lead to benefit in long-term outcomes such as chronic lung disease. However, follow-up into childhood is needed to inform later outcomes of treatment.

Our study protocol did not allow the use of other prenatal interventions, such as tocolysis, so that we could determine whether the difference in the primary outcome was due to the use of antenatal betamethasone. Although we delayed augmentation of labor by means of oxytocin by 12 hours for women with ruptured membranes who had contractions or whose cervical dilation was 3 cm or more, we did not find a significant between-group difference in the rates of maternal or neonatal infectious complications.

In conclusion, the administration of antenatal betamethasone in women at risk for late preterm delivery significantly decreased the rate of respiratory complications in newborns. Betamethasone administration significantly increased the rate of neonatal hypoglycemia but not the rates of other maternal or neonatal complications.

The views expressed in this article are those of the authors and do not necessarily represent the views of the NICHD or the National Heart, Lung, and Blood Institute (NHLBI).

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APPENDIX

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