OBSTETRICS

Are newborn outcomes different for term babies who were exposed to antenatal corticosteroids?

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BACKGROUND: Antenatal corticosteroids improve newborn outcomes for preterm infants. However, predicting which women presenting for threatened preterm labor will have preterm infants is inaccurate, and many women receive antenatal corticosteroids but then go on to deliver at term.

OBJECTIVE: This study aimed to compare the short-term outcomes of infants born at term to women who received betamethasone for threatened preterm labor with infants who were not exposed to betamethasone in utero.

STUDY DESIGN: We performed a retrospective cohort study of infants born at or after 37 weeks' gestational age to mothers diagnosed as having threatened preterm labor during pregnancy. The primary neonatal outcomes of interest included transient tachypnea of the newborn, neonatal intensive care unit admission, and small for gestational age and were evaluated for their association with betamethasone exposure while adjusting for covariates using multiple logistic regression.

RESULTS: Of 5330 women, 1459 women (27.5%) received betamethasone at a mean gestational age of 32.2±3.3 weeks. The mean age of women was 27±5.9 years and the mean gestational age at delivery was 38.9±1.1 weeks. Women receiving betamethasone had higher rates of maternal comorbidities ($P<.001$ for diabetes mellitus, asthma, and hypertensive disorder) and were more likely to self-identify as White ($P=.022$). Betamethasone-exposed neonates had increased rates of transient tachypnea of the newborn, neonatal intensive care unit admission, small for gestational age, hyperbilirubinemia, and hypoglycemia (all, $P<.05$). Controlling for maternal characteristics and gestational age at delivery, betamethasone exposure was not associated with a diagnosis of transient tachypnea of the newborn (adjusted odds ratio, 1.10; 95% confidence interval, 0.80—1.51), although it was associated with more neonatal intensive care unit admissions (adjusted odds ratio, 1.49; 95% confidence interval, 1.19—1.86) and higher odds of the baby being small for gestational age (adjusted odds ratio, 1.78; 95% confidence interval, 1.48—2.14).

CONCLUSION: Compared with women evaluated for preterm labor who did not receive betamethasone, women receiving betamethasone had infants with higher rates of neonatal intensive care unit admission and small for gestational age. Although the benefits of betamethasone to infants born preterm are clear, there may be negative impacts for infants delivered at term.

Key words: antenatal corticosteroids, growth, newborn outcomes, NICU admission

Introduction

A course of antenatal corticosteroids, such as betamethasone (BMZ), is typically administered to pregnant women between 24 and 36+6/7 weeks' gestation at risk of delivery within 7 days.[1] Antenatal corticosteroids accelerate fetal lung development, subsequently leading to decreased rates of respiratory distress syndrome, respiratory support needed, and intensive care admission and decreased incidence of complications common to preterm neonates, such as intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death.[2]

However, predicting which women presenting with threatened preterm labor will actually deliver before term is still inexact owing to the inaccuracy of existing markers and the lack of understanding of underlying mechanisms.[3] Many women diagnosed as having threatened preterm labor are given antenatal corticosteroids but do not deliver until they reach term (≥37 weeks).[4]

It is unclear whether exposure to antenatal corticosteroids for these term infants is beneficial or may lead to some harm. There are data demonstrating potential worsening lung function in infants exposed to antenatal corticosteroids.[5,6] Thus, the imperative to give antenatal corticosteroids to women in threatened preterm labor quickly may not be prudent for those who go on to deliver at term.

This study aimed to compare the short-term outcomes of infants born at term (at least 37 weeks' gestation) to women who received BMZ injections for threatened preterm labor with infants who were not exposed to BMZ in utero but whose mothers were also evaluated for threatened preterm labor.

Materials and Methods

This study was a retrospective cohort study. The cohort consisted of babies born in Indianapolis, IN, in Indiana University Health hospitals and Eskenazi Hospital from 2012 to 2019 at or after 37 weeks' gestation to mothers who had been evaluated for and diagnosed as having threatened preterm labor at some point during pregnancy. These dates were chosen based on the availability of electronic medical record (EMR) data. The cohort was restricted to singleton infants born at term. Of primary interest was the comparison of infants born at term who were exposed to maternal BMZ therapy for threatened preterm labor and infants born at term whose mothers had been seen in an acute

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AJOG at a Glance

Why was this study conducted?

Women evaluated for threatened preterm labor are frequently given antenatal corticosteroids but then go on to deliver at term. It is unclear whether this exposure to a single course of steroids has beneficial or harmful impacts on the term newborn.

Key findings

Compared with term newborns from women who were evaluated for threatened preterm labor but not given steroids, those newborns whose mothers were given steroids had higher rates of newborn intensive care unit admission and being small for gestational age, without any difference in rates of transient tachypnea of the newborn.

What does this add to what is known?

The use of antenatal corticosteroids for women being evaluated for threatened preterm labor should be judicious, because this study demonstrates in a large, diverse population that there may be associated adverse outcomes for exposed newborns who go on to deliver at term.

setting for threatened preterm labor but did not receive BMZ therapy.

Data for this study were collected from the EMR system data warehouse (Epic and Cerner) in deidentified fashion through the EMR data brokers at the Regenstrief Institute (Indianapolis, IN). Regenstrief then extracted the variables of interest from pharmacy records, discreet fields within the EMR, and diagnostic codes (International Classification of Diseases, Ninth and Tenth Revisions). Maternal variables included age at the time of infant delivery, race or ethnicity, smoking status during pregnancy, date of BMZ injection, due date, maternal history of asthma, preexisting or gestational diabetes mellitus, chronic hypertension, and hypertensive disorder of pregnancy. Short-term neonatal characteristics included gestational age at birth, date of birth, birthweight, birth length, birth head circumference, neonatal intensive care unit (NICU) admission, intubation, jaundice needing treatment, transient tachypnea of the newborn (TTN) diagnosis, oxygen support, treated hypoglycemia, and meconium aspiration syndrome diagnosis.

The primary neonatal outcomes of interest were TTN diagnosis, NICU admission, and small for gestational age (SGA). The original analysis plan created before data extraction included TTN diagnosis, oxygen use, and birth length. However, after manual chart review, the hospital coding for oxygen use was not found to be accurate; thus, NICU admission was included as a primary outcome instead. In addition, SGA was included as the primary outcome instead of birth length because SGA is known to be more clinically meaningful. SGA was categorized by the published revised United States birthweight reference published by Duryea et al.[7] After data were extracted, a selection of random infants with exposure to BMZ and infants without exposure to BMZ ($\sim$1%) had manual data abstraction for data validation and verification to ensure that the diagnoses and codes were correct in the medical record. The study was approved by the local governing institutional review board and the scientific review group at the Regenstrief Institute Data Core.

Baseline characteristics were summarized for the entire cohort and by BMZ exposure status. Characteristics were compared between exposure groups using appropriate statistical tests (ie, Chi-square and *t* tests). Multivariable logistic regression was employed to determine whether BMZ exposure was independently associated with each neonatal outcome after adjusting for baseline characteristics. Regression models included factors known to contribute to newborn and long-term health outcomes (maternal age, socioeconomic status [insurance], race, and estimated gestational age [EGA] at delivery) and also factors that were found to significantly differ ($P<.05$) between exposure groups. To assess for the presence of collider bias with EGA at delivery, we repeated the regression excluding EGA at delivery as a variable. All data were incorporated into RedCap and analyzed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Although an a priori sample size was not specifically calculated, based on initial database queries before data extraction, we anticipated data on at least 1500 women who received steroids and delivered after 37 weeks were estimated. Assuming that approximately 10% of babies were admitted to the NICU, a sample of 3000 women (half of whom received BMZ) would have 80% power to detect a change in the proportion with NICU admission from 10% to 13.7%, corresponding to an adjusted odds ratio (aOR) of 1.43, based on a logistic regression model adjusting for covariates. Even smaller odds ratios would be detectable if the proportion of nonexposed women was actually larger.

Human subjects' protection and data management: All investigators associated with this study passed the Certifications in Human Subjects Protections for human subjects. All data were stored in a secured RedCap database, analytical files were deidentified, and all computers used were password protected. Regenstrief data security policies were employed during data extraction. As a retrospective cohort study, a data safety monitoring board was not required.

Results

Of 5330 women identified in the cohort, 1459 (27.4%) received BMZ (Table 1). The majority of the population were not Hispanic or Latino (92.0%) and were White (71.4%). Approximately 55% of women were insured by Medicaid or Government Insurance, whereas 43.4% had private insurance. The mean age of the women was 27$\pm$5.9 years. Women who did not receive BMZ were evaluated

TABLE 1
Selected maternal and neonatal characteristics of cohort

	Overall cohort (N=5330)	BMZ-exposed (n=1459)	BMZ not exposed (n=3871)	*P* value
Maternal characteristics				
Age (y), mean (SD)	27.0 (5.9)	27.5 (6.0)	26.8 (5.8)	<.001
Ethnicity				
Hispanic or Latino	329 (6.2)	90 (6.2)	239 (6.2)	.811
Not Hispanic or Latino	4903 (92.0)	1345 (92.2)	3558 (91.9)	
Unknown	98 (1.8)	24 (1.6)	74 (1.9)	
Race				
Black	1204 (22.6)	292 (20.0)	912 (23.6)	.022
White	3803 (71.4)	1077 (73.8)	2726 (70.4)	
Other/unknown	323 (6.1)	90 (6.2)	233 (6.0)	
Insurance				
Medicaid/government	2941 (55.2)	785 (53.8)	2156 (55.7)	.125
Private	2315 (43.4)	647 (44.3)	1668 (43.1)	
None	74 (1.4)	27 (1.9)	47 (1.2)	
Maternal diabetes mellitus, yes	326 (6.1)	139 (9.5)	187 (4.8)	<.001
Maternal asthma, yes	144 (2.7)	78 (5.3)	66 (1.7)	<.001
Maternal hypertensive disorder, yes	584 (11.0)	365 (25.0)	219 (5.7)	<.001
EGA when they received BMZ or were evaluated for threatened preterm labor, mean (SD)	32.8 (4.6)	32.2 (3.3)[a]	33.0 (5.0)	
Neonatal characteristics				
EGA at delivery (wk), mean (SD)	38.9 (1.1)	38.4 (1.1)	39.1 (1.1)	<.001
Birth length (cm), mean (SD)	52.0 (77.6)	50.5 (17.4)	52.6 (90.3)	.179
Head circumference at birth (cm), mean (SD)	34.3 (9.5)	33.9 (9.1)	34.4 (9.7)	.128
Birthweight (g), mean (SD)	3289.9 (497.4)	3153.8 (575.9)	3341.1 (454.1)	<.001

Values are number (percentage) unless indicated otherwise.

BMZ, betamethasone; *EGA*, estimated gestational age; *SD*, standard deviation.

[a] The gestational age for women who did not receive BMZ at the time of evaluation for threatened preterm labor is provided. This is provided for descriptive purposes only and not considered as a covariate because it is not directly comparable between exposure groups.

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for threatened preterm labor at a mean gestational age of 33.0±5.0 weeks, whereas women in the BMZ group received the medication at a lower gestation age of 32.2±3.3 weeks. Women receiving BMZ had higher rates of maternal comorbidities ($P<.001$ for diabetes mellitus, asthma, and hypertensive disorder) and were more likely to self-identify as White ($P=.022$) (Table 1). Ethnicity did not differ between exposure groups and was not included in regression models. Maternal smoking status was extracted to use as a covariate but was missing for 49.5% of women and thus was not included in any analyses. Neonatal characteristics considered as potential covariates included EGA at birth. Birth length, head circumference, and birthweight are provided as descriptive only because they are highly related to SGA (Table 2). Infants were delivered at a mean EGA of 38.9±1.1 weeks with a mean birthweight of 3289.9±497.4 grams, birth length of 52.0±77.6 cm, and head circumference of 34.3±9.5 cm. Women who received BMZ delivered babies at a slightly earlier EGA (38.4±1.1 vs 39.1±1.1) ($P<.001$). Birth length and head circumference at birth did not markedly differ between exposure groups.

From the unadjusted analysis of outcomes, BMZ-exposed infants had higher rates of TTN diagnosis and NICU admission ($P<.05$) (Table 2). Based on the tenth percentile birthweight threshold, 19.6% of infants in the BMZ exposure group were considered SGA, whereas 12.2% of infants in the nonexposed group were considered SGA ($P<.001$) (Table 2). BMZ-exposed

TABLE 2
Primary and secondary neonatal short-term outcomes

Primary outcomes	Overall cohort (N=5330)	BMZ-exposed (n=1459)	BMZ not exposed (n=3871)	*P* value	
Diagnosis of TTN, yes	215 (4.0)	74 (5.1)	141 (3.6)	.018	
NICU admission, yes	426 (8.0)	179 (12.3)	247 (6.4)	<.001	
Small for gestational age, yes	N=4905 699 (14.3)	n=1340 263 (19.6)	n=3565 436 (12.2)	<.001	
Secondary outcomes				*P* value	*P* value[a]
Intubation, yes	42 (0.8)	13 (0.9)	29 (0.7)	.601	.975
Hyperbilirubinemia requiring treatment, yes	806 (15.1)	244 (16.7)	562 (14.5)	.045	.169
Treated hypoglycemia newborn, yes	216 (4.1)	96 (6.6)	120 (3.1)	<.001	<.001
Meconium aspiration syndrome, yes	23 (0.4)	5 (0.3)	18 (0.5)	.544	.957

Values are number (percentage) unless indicated otherwise.

BMZ, betamethasone; *NICU*, neonatal intensive care unit; *TTN*, transient tachypnea of the newborn.

[a] *P* value adjusted for multiple secondary outcomes with Šidák adjustment.

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infants also had higher rates of hyperbilirubinemia and hypoglycemia (all, $P<.05$). Exposure groups did not substantially differ on intubation or meconium aspiration syndrome. After adjusting for multiple comparisons for the 4 secondary outcomes, BMZ-exposed infants were still more likely to be treated for hypoglycemia than nonexposed infants (Table 2).

After adjusting for maternal age, race, insurance, maternal conditions (diabetes mellitus, asthma, and hypertensive disorder), and EGA at delivery, there was no significant difference in TTN diagnosis between BMZ exposure and BMZ nonexposure groups (aOR, 1.10, 95% confidence interval [CI], 0.80−1.51) (Table 3). Infants from women who self-identified their race as either other or unknown were more likely to be diagnosed as having TTN than those born to White women (aOR, 1.70; 95% CI, 1.04−2.77), and infants delivered at later gestational ages were less likely to have a TTN diagnosis (aOR, 0.74; 95% CI, 0.65−0.84).

Infants from the BMZ exposure group were more likely to be admitted to the NICU (aOR, 1.49; 95% CI, 1.19−1.86), as were those born to mothers with maternal diabetes mellitus (aOR, 1.50; 95% CI, 1.06−2.12) or with Medicaid or government insurance (aOR, 1.42; 95% CI, 1.14−1.76). Infants whose mothers were Black were less likely to be admitted to the NICU than those whose mothers were White (aOR, 0.76; 95% CI, 0.58−0.99). Infants born at later gestational ages (aOR, 0.63; 95% CI, 0.57−0.70) were also less likely to be admitted to the NICU (Table 3).

The adjusted analysis (Table 3) also demonstrated that infants in the BMZ exposure group were more likely to be classified as SGA than infants in the nonexposure group (aOR, 1.78; 95% CI, 1.48−2.14). Infants whose mothers self-identified their race as Black (aOR, 1.80; 95% CI, 1.50−2.16) or other/unknown (aOR, 1.69; 95% CI, 1.24−2.32) were more likely to be SGA than those born to White women. In addition, mothers covered by Medicaid/government insurance were more likely to have infants classified as SGA (aOR, 1.29; 95% CI, 1.07−1.53).

The logistic regression for all 3 outcomes excluding EGA at delivery from the covariates is presented in the Supplemental Table. The associations with the 3 outcomes were not appreciably different.

Comment

Principal findings

Our results demonstrate that preterm antenatal exposure to BMZ for term-born neonates was associated with increased odds of NICU admission and SGA birthweights, but was not associated with increased odds of TTN after adjusting for clinical covariates. This points to a potential adverse impact of the current practice trend of administering antenatal corticosteroids with a low threshold to women being evaluated for threatened preterm birth.

Results in context

Because so many women evaluated for threatened preterm birth do not deliver until term, the ability to prudently initiate interventions is important, given these results. In 1 study of 763 women who had unscheduled triage visits for symptoms of preterm labor, only 18% gave birth before 37 weeks' gestation and only 3% gave birth within 2 weeks of presenting with symptoms.[8] Better tools are needed for women presenting with threatened preterm labor to determine who will be at the highest risk to deliver within 7 days and thus should receive antenatal corticosteroids.[1]

Our results, showing increased rates of SGA infants, are consistent with other literature showing the same adverse impact of multiple courses of antenatal steroids.[9,10] These impacts have also been demonstrated in animal models.[4] In addition, a similar study also found

TABLE 3
Logistic regression of primary outcomes, adjusted for covariates

		N=5330 (TTN, 4%)	n=5311 (NICU, 8%)	n=4905 (SGA, 14.3%)
Covariate	Comparison	Diagnosis of TTN aOR (95% CI)	NICU admission aOR (95% CI)	SGA aOR (95% CI)
BMZ group	BMZ exposure vs no exposure	1.10 (0.80–1.51)	1.49 (1.19–1.86)	1.78 (1.48–2.14)
Maternal age	1-y increase	0.98 (0.96–1.01)	1.00 (0.98–1.02)	0.97 (0.96–0.99)
Race	Black vs White	1.01 (0.72–1.42)	0.76 (0.58–0.99)	1.80 (1.50–2.16)
	Other/unknown vs White	1.70 (1.04–2.77)	0.91 (0.59–1.40)	1.69 (1.24–2.32)
	Black vs other/unknown	0.59 (0.33–1.02)	0.84 (0.52–1.35)	1.06 (0.76–1.48)
Insurance	Medicaid/government vs private	1.30 (0.96–1.76)	1.42 (1.14–1.76)	1.29 (1.07–1.53)
	None vs private	1.20 (0.37–3.94)	0.20 (0.03–1.43)	1.25 (0.64–2.44)
	Medicaid/government vs none	1.08 (0.33–3.50)	7.21 (0.99–52.46)	1.03 (0.53–1.99)
Maternal diabetes mellitus	Yes vs no	1.27 (0.77–2.11)	1.50 (1.06–2.12)	0.92 (0.64–1.31)
Maternal asthma	Yes vs no	1.25 (0.60–2.61)	0.91 (0.50–1.64)	1.39 (0.90–2.14)
Maternal hypertensive disorder	Yes vs no	1.10 (0.72–1.68)	0.92 (0.68–1.25)	0.86 (0.66–1.14)
EGA at delivery	1-wk increase	0.74 (0.65–0.84)	0.63 (0.57–0.70)	0.93 (0.86–1.00)

Adjustments made for all other variables in the table.

aOR, adjusted odds ratio; *BMZ*, betamethasone; *CI*, confidence interval; *EGA*, estimated gestational age; *NICU*, neonatal intensive care unit; *SGA*, small for gestational age; *TTN*, transient tachypnea of the newborn.

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an increased rate of SGA infants exposed to antenatal corticosteroids who delivered at term (11% vs 6%), although that study's control group included all women delivering at term.[11] By limiting our control group to women evaluated for threatened preterm labor, we attempted to have a control group with similar pregnancy experiences to the women who received BMZ but delivered at term. Although threatened preterm birth has been associated with fetal growth abnormalities,[12] we have demonstrated that exposure to BMZ may increase rates of SGA beyond that for control women evaluated for threatened preterm birth. Because it is known that SGA infants have higher rates of adverse health conditions later in life such as hypertension and metabolic issues, this antenatal exposure could be contributing to adverse health consequences.

Our results showing that Black babies had lower rates of NICU admission but higher rates of SGA were unexpected. It is known that there are disparities in newborn care and outcomes in both preterm and term infants by race.[13,14] Given the disparities in infant mortality in the United States, it is important to further explore our results and the implications for care of Black women with threatened preterm birth.

Clinical implications

Given the known benefits to BMZ for preterm infants and the difficulty in predicting which women will actually deliver preterm, it is common for providers to administer antenatal corticosteroids in an effort not to miss the opportunity to give them before delivery and to try and get the maximal time benefit. However, because many of these babies will be born at term and may have adverse outcomes as we have demonstrated, it may be wise to use BMZ more judiciously for women who are evaluated for threatened preterm birth. This is particularly true because they are recommended for threatened late preterm birth as well.

Research implications

Developing a more robust method to determine which women who present in threatened preterm labor will actually deliver within 1 to 2 weeks should continue to be a research priority. In addition, a tool which would trigger a woman to be in a "high risk to deliver" category that would then be accompanied by BMZ administration could aid clinicians with this decision. Furthermore, a better understanding of the disparities in outcomes from these newborns and any differential impact that antenatal corticosteroids may have, accounting for social determinants of health, will be important. Replicating these findings in other populations will be important.

Strengths and limitations

Given the large number of women in both groups and the diversity of our population, we believe our results may be generalizable. Our study was limited in its retrospective nature and its reliance upon medical record and coding data. However, the Regenstrief Institute has a proven track record with this kind of work, and the accuracy of the retrieved data has been well documented.[15,16] Another limitation is that we do not know what information the provider

used to aid in the decision to provide the BMZ injections other than that obtained from the medical record. NICU admission alone does not herald future health; however, it has been demonstrated that infants admitted to the NICU do have increased rates of adverse health outcomes, even when limited to term births.[17,18] We were unable to determine whether any of the women in the BMZ group had received more than 1 course of BMZ. There is also the possibility of these associations being confounded by some unknown variable.

Conclusions

Infants born at term may be at an increased risk for NICU admissions and SGA if they were exposed to antenatal corticosteroids during their development. These early neonatal outcomes can be markers for future infant health. Because providers have difficulties determining which patients evaluated for threatened preterm birth will actually deliver before term, caution may need to be taken before giving antenatal corticosteroids. ■

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SUPPLEMENTAL TABLE

Logistic regression of primary outcomes, adjusted for covariates, not including estimated gestational age at delivery

		N=5330 (TTN, 4%)	n=5311 (NICU, 8%)	n=4905 (SGA, 14%)
Covariate	Comparison	Diagnosis of TTN, aOR (95% CI)	NICU admission, aOR (95% CI)	SGA, aOR (95% CI)
BMZ group	BMZ exposure vs no exposure	1.32 (0.97–1.79)	1.94 (1.57–2.40)	1.87 (1.56–2.23)
Maternal age	1-y increase	0.99 (0.96–1.01)	1.00 (0.99–1.02)	0.97 (0.96–0.99)
Race	Black vs White	1.00 (0.72–1.41)	0.76 (0.58–0.98)	1.80 (1.49–2.16)
	Other/unknown vs White	1.68 (1.03–2.72)	0.90 (0.58–1.38)	1.68 (1.23–2.31)
	Black vs other/unknown	0.60 (0.35–1.03)	0.84 (0.53–1.35)	1.07 (0.76–1.49)
Insurance	Medicaid/government vs private	1.32 (0.97–1.79)	1.44 (1.15–1.79)	1.28 (1.07–1.54)
	None vs private	1.15 (0.35–3.75)	0.18 (0.03–1.34)	1.22 (0.63–2.39)
	Medicaid/government vs none	1.15 (0.36–3.70)	7.79 (1.08–56.49)	1.05 (0.54–2.03)
Maternal diabetes mellitus	Yes vs no	1.44 (0.87–2.38)	1.76 (1.25–2.48)	0.94 (0.66–1.35)
Maternal asthma	Yes vs no	1.23 (0.59–2.57)	0.89 (0.49–1.59)	1.38 (0.90–2.13)
Maternal hypertensive disorder	Yes vs no	1.30 (0.86–1.97)	1.19 (0.89–1.60)	0.90 (0.69–1.18)

Adjustments made for all other variables in the table.

aOR, adjusted odds ratio; *BMZ*, betamethasone; *CI*, confidence interval; *EGA*, estimated gestational age; *NICU*, neonatal intensive care unit; *SGA*, small for gestational age; *TTN*, transient tachypnea of the newborn.

McKinzie et al. Outcomes for term newborns exposed to corticosteroids. Am J Obstet Gynecol 2021.