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# Long-term childhood outcomes for babies born at term who were exposed to antenatal corticosteroids

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## Abstract

**Background:** Antenatal corticosteroids (ACS) improve neonatal outcomes when administered to infants who are at risk of preterm delivery. Many women who receive ACS for threatened preterm labor go on to deliver at term. Thus, long-term outcomes should be evaluated for term-born infants who were exposed to ACS in-utero

**Objective:** The objective of this study was to compare the long-term outcomes of term-born children at least 5 years of age who were born to women who received ACS for threatened preterm labor, compared to children whose mothers were also evaluated for threatened preterm labor but did not receive ACS.

**Study Design:** We performed a retrospective cohort study of children born at or after 37 weeks' gestational age, who are now at least 5 years of age, born to mothers diagnosed with threatened preterm labor during pregnancy. The primary exposure of interest was receiving ACS. Among the collected childhood medical conditions, the primary outcome of interest was a diagnosis of asthma.

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**Results:** Of 3,556 women having a term-born child at least 5 years old, 629 (17.6%) were exposed to antenatal corticosteroids (all betamethasone) and 2,927 (82.3%) were controls whose mothers were evaluated for threatened preterm birth but did not get ACS injections. Women receiving ACS had higher rates of maternal comorbidities (diabetes, hypertension) (p ≤ 0 01). ACS-exposed children had no difference in diagnosis of asthma (12.6% vs 11.6%), attention deficit disorder, or developmental delay (p=0.47, 0.54, 0.10 respectively). Controlling for maternal and neonatal characteristics, asthma was not different between those exposed to ACS compared to controls (OR 1.05, 95% CI 0.79, 1.39). The odds of the child's weight percentile being <10% was increased for ACS-exposed children born at term (OR 2.00, 95% CI 1.22, 3.25).

**Conclusions:** Babies born at term who were exposed to ACS may have increased odds of being in a lower growth percentile than those not exposed. However, rates of diagnoses such as asthma, developmental delay, and attention deficit disorders were not different.

## Condensation:

Babies born at term who were exposed to antenatal corticosteroids may have increased rates of being in a lower childhood growth percentile than those not exposed.

### Keywords

Antenatal Corticosteroids (ACS); asthma; attention deficit disorder; developmental delay; growth percentile; threatened preterm birth; weight percentile

## Background

Antenatal corticosteroids (ACS) are recommended standard of care for pregnant women between 24 and 36 6/7 weeks gestational at risk of delivery within 7 days[1]. The neonatal benefits of ACS are clear; ACS reduce morbidity and mortality for infants born preterm[2, 3]. Corticosteroids accelerate maturation of a number of organ systems, most importantly, fetal lungs.(3)

Women diagnosed with threatened preterm labor often receive ACS but subsequently go on to deliver at term (>= 37 weeks)[4]. Long term outcome studies of infants who received ACS and subsequently delivered before term are encouraging; yet there remains the possibility that structural changes induced by corticosteroid in the perinatal period may have long-term adverse effects on lung function later in life[5–8]. Recent data from infants born at term (at least 37 weeks gestation) and exposed to ACS suggest a potential worsening of infant lung function and increased rates of small for gestational age (SGA) infants and neonatal intensive care unit admissions[9, 10]. Thus, it is imperative that long-term outcomes be evaluated for term-born infants who were exposed to ACS in-utero.

The objective of this study was to compare the long-term outcomes of children at least 5 years of age who were born at term to women who received ACS for threatened preterm labor, compared to children whose mothers were also evaluated for threatened preterm labor but did not receive ACS. The primary outcome of interest was asthma. Our hypothesis was that for these term-born children, exposure to ACS in utero would have adverse effects, particularly on respiratory outcomes.

## Methods

This study was a retrospective cohort study of children born in Indianapolis, IN in Indiana University Health Hospitals from 2012–2014 at or after 37 weeks' gestation to mothers who had been evaluated for and diagnosed with threatened preterm labor at some point during their pregnancy. The dates were limited in this way to ensure that the children were at least 5 years old at the time of the data pull in 2020. This was because that was an age at which many of the diagnoses of interest would be made. The cohort was restricted to singleton infants born at term. Children were considered exposed to antenatal corticosteroids if their mother had received either betamethasone or dexamethasone during the pregnancy. Control infants had mothers who were evaluated for threatened preterm labor during the pregnancy but did not receive ACS.

Data for this study were collected from the electronic medical record (EMR) system data warehouse (Cerner) in a de-identified 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 (ICD9/10). The processes used by the Regenstrief Institute have been reported elsewhere[11, 12]. The population of women evaluated for threatened preterm labor was from ICD9/10 codes (ICD-9 644.0X, 644.1X or ICD-10 O60.0X, O60.22X, O60.23X). The date of the evaluation was confirmed to be during a registered pregnancy in the system. The date of betamethasone or dexamethasone injections were taken from pharmacy orders and records and compared to pregnancy dates and the date of evaluation for threatened preterm labor for validity. We then limited the data to children who were at least 5 years old who had an encounter with the health system in the EMR after their 5$^{th}$ birthday. This encounter could have been a primary care visit, acute visit, or hospital visit.

Maternal variables extracted included age at the time of delivery, ethnicity and race, insurance status, pre-existing diabetes, chronic hypertension, development of gestational diabetes or hypertensive disorder of pregnancy, and gestational age when the woman received ACS (cases) or was evaluated for threatened preterm labor (controls).

The primary outcome of interest was a diagnosis of asthma. Outcomes collected for the children included gestational age at birth, birth weight, birth length, birth head circumference, and childhood diagnoses of attention deficit disorder (ADD), hypoxemia, tachypnea, wheezing, albuterol prescription, bronchiolitis, developmental delay, diabetes, number of hospitalizations, BMI percentile, Height/length percentile, weight percentile. Diagnoses were from ICD9/10 codes in the EMR. Any hospitalizations were also recorded. Growth percentiles were calculated from published sex-specific growth curves from recorded characteristics from pediatric or other primary care visits[13]. Dates of the records were then compared to date of birth to calculate the child's age.

After data were extracted, a selection of random infants with exposure to ACS and infants without exposure to ACS (~1%) had manual data abstraction for data validation/verification to ensure that the diagnoses and codes were correct in the medical record. The local

governing IRB and the scientific review group at the Regenstrief Institute Data Core approved the study.

### Data analysis

Baseline characteristics were summarized for the entire cohort and by ACS exposure status. Characteristics were compared between exposure groups using appropriate statistical tests (i.e. chi-square and t-tests). We utilized an unmatched control group for the analyses. Multivariable logistic regression was employed to determine if ACS exposure was independently associated with each childhood outcome after adjusting for baseline characteristics. Regression models included ACS group or control and maternal and neonatal factors found to be different between the groups. All data were incorporated into a RedCap database and analyzed using SAS Version 9.4 (Cary, NC).

### Sample Size

We did not perform an a priori sample size calculation. We used a sub cohort from a previous study evaluating short-term newborn outcomes in the same population. We limited this larger cohort to children who were at least 5 years old. As this was exploratory with a primary outcome of asthma diagnosis, if we assumed a 10% rate of asthma diagnosis in controls and 15% in ACS-exposed children, and knowing that in the larger cohort, the ratio of ACS exposed pregnancies to controls was 1:3, we would have 80% power to detect this difference with a group of 440 ACS-exposed children and 1320 control children who were not exposed. We based these assumptions on asthma rates seen in our clinical population, similar to published rates[14], and clinical expertise on expectations of increased rates of asthma. When limiting the larger cohort as noted above, we had a population large enough to satisfy these assumptions.

Human subjects protection and data management: all investigators associated with this study passed the CITI human subjects certification. All data were stored in a secured RedCap database, analytic files were de-identified, and all computers 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 3,556 women identified in the cohort of term-born children at least 5 years old, 629 (17.6%) were exposed to ACS (all betamethasone) and 2,927 (82.3%) were controls whose mothers were evaluated for threatened preterm birth but did not receive ACS injections. Maternal characteristics of the groups are included in Table 1. Maternal age was younger for he ACS exposed group (mean 27.2±5.9 vs. 36.5±5.8 years-old, p=0.003). The groups had clinically similar gestational ages when they received ACS or were evaluated for threatened preterm birth, although the difference was statistically significant (31.4±3.0 vs. 31.9±4.8 weeks, p=0.01). Mean number of weeks between the preterm birth evaluation and delivery were similar at just over 7 weeks (p=0.62). Other characteristics were similar, with the exception of more women in the ACS-exposed group having a diagnosis of maternal diabetes (4.8% vs 2.8%, p=0.01) and hypertensive disorders of pregnancy (19.4% vs. 6.0%,

p<0.001). The children were a mean of 7 years old at the time of the data pull in the summer 2020 (Table 1, p=0.617). There were statistically significant differences between the groups for their birth characteristics regarding gestational age at delivery, birth length, head circumference, and birth weight (all p<0.001), but none of these differences were clinically significant. The rate of SGA infants (birth weight percentile <10%) was higher for women who received ACS (21.8% vs. 16.4%, p=0.005).

Outcomes and characteristics of the children in each group are presented in Table 2. The primary outcome of interest was diagnosis of asthma. There was no clear difference in rates of childhood asthma between the ACS exposed group vs. not exposed (12.6% vs 11.6%, p 0.402). Additionally, no statistically significant differences were observed between outcomes amongst other respiratory conditions such as wheezing (7.8% vs. 8.0%, p 0.864), albuterol prescription (22.1% vs. 22.6%, p 0.792), and bronchiolitis (18.1% vs 16.7%, p 0.402). There were also no differences between diagnoses of ADD (3.2% vs. 2.7%, p 0.539) or developmental delay (8.1% vs 6.3%, p 0.102). The rate of children measuring <10$^{th}$ percentile on growth curves was higher in those who were exposed to ACS (13.7% vs 7.1%, p=0.001)

The multivariable model included maternal age, gestational age at delivery, and maternal diabetes and hypertensive disorders of pregnancy, SGA, in addition to whether they were exposed to ACS in utero or not (Table 3). Asthma was inversely associated with maternal age and gestational age at delivery (OR 0.97, 95% CI 0.95, 0.98 and OR 0.84, 95% CI 0.76, 0.93, respectively). Asthma was not different between those exposed to ACS compared to controls (OR 1.05, 95% CI 0.79, 1.39). The child's weight percentile <10% was significantly increased for ACS-exposed children born at term (OR 2.00, 95% CI 1.22, 3.25).

## Comment

### Principle Findings

We did not find a difference in rates of asthma between children born at term who were or were not exposed to ACS in utero for threatened preterm birth. We found that children born at term who were exposed to ACS had an increased odds of a secondary outcome of being at <10$^{th}$ % weight compared to children who were not exposed. These increased odds remained, even when adjusting for being SGA at birth. This finding is consistent with observations of the impact of ACS on fetal growth and newborn growth percentiles, particularly after exposure to repeated courses[15–17]. Given that we are unaware of other reports limited to term-born babies, this finding may warrant caution for clinicians and further investigation.

### Clinical and Research Implications

Studies that examine the impact of ACS, particularly repeat doses, did not show a decrease in perinatal or neonatal mortality but did show lower birth weights, small head circumferences and shorter birth lengths[17–19]. Several studies report significant difference in body size at birth between cohorts of infants exposed to ACS vs. infants with no exposure.

Fetal growth is a known potential marker for fetal programming and has been associated with increased rates of coronary heart disease and related disorders, such as stroke, hypertension and diabetes[20]. This difference in growth may indicate a transient effect of corticosteroids on growth with a "catch-up" period following birth. However, there are data that indicate a number of permanent changes in physiologic function based on modification of the prenatal environment that are mediated through epigenetic processes[21, 22]. The effects of this altered environment in utero may not manifest until childhood, adolescence or even adulthood. This highlights the importance of studies like the current one that examine longer-term impacts.

It is a core concept that corticosteroids are delivering a stress signal to fetuses normally exposed to low levels of glucocorticoids, which potentially may change developmental pathways and lead to consequences for long-term chronic diseases or adverse neurodevelopmental outcomes. While not necessarily powered to detect such small differences, our results are reassuring that the effects of ACS in utero show no statistically significant differences in longer term outcomes such as asthma, developmental delay, or ADD in term born babies. This is in accordance with other data evaluating long-term outcomes of lung function in ACS exposed cohorts who delivered preterm[7]. Alternatively, animal models provide evidence that prenatal exposure to glucocorticoids alters fetal brain development; subsequently impacting behavior. A recent study from Finland also noted a hazard ratio of 1.47 (95%CI 1.36–1.60) of any mental or behavioral disorder in children born at term who were exposed to ACS.[23] Fetal exposure to elevated levels of maternal cortisol is one proposed mechanism for the development of ADHD[24]. However, it is reassuring that no statistically significant differences were detected with the development of ADD in our study, which consisted of children with a mean age of 7, an age by which ADD is typically diagnosed. These outcomes point to the likely long-term safety of use of ACS in pregnancy for many childhood outcomes.

## Results in the context of what is known

While ACS are one of the most important advances in perinatal medicine delivered to expectant mothers in anticipation of preterm birth, approximately 50% of women given one course of ACS remain pregnant 7–14 days later, which is outside the optimal therapeutic window[21]. Many of these women go on to deliver at term. While our results are reassuring in demonstrating no differences in most long-term outcomes in early childhood who delivered at term, we did find that children exposed to ACS in utero were at increased odds of being $<10^{th}$ % in weight, which may herald the potential for adverse outcomes in later adolescence or adulthood, which were not evaluated in this study. This suggests that providers should consider potential consequences to administering ACS and highlights further areas of research to determine which women diagnosed with threatened preterm labor are at the highest risk for delivery within 1–2 weeks. There may be a need for more judicious use of ACS in women who may not be likely to deliver until term.

There is accumulating evidence that episodes of threatened preterm labor may be risk factors for adverse outcomes alone.[25] Term delivered neonates from pregnancies with an episode of suspected preterm labor had higher rates of SGA.[26–28] The mechanism behind these findings

has been examined and are believed to be related to underperfusion from maternal vascular lesions leading to utero-placental ischemia.[25, 29] Additionally, gene expression in placentae of term births that were evaluated for threatened preterm birth have altered gene expression patterns.[30, 31] Here, our work has tried to elucidate one of the components of evaluations for threatened preterm birth, the administration of ACS. Our findings that exposure to ACS during threatened preterm labor evaluations increased rates of SGA at birth[32] and also lower childhood growth percentiles later in life, even controlling for SGA at birth, add to the literature in this field, indicating that the administration of ACS may be important in the mechanistic pathway. While ACS are known to suppress fetal adrenal function[33], the long-term mechanistic implications related to childhood growth need to be further studied.

### Strengths and Limitations

This study is subject to limitations common to queries from clinical EMR such as misclassification, under-reporting, and data errors. The Regenstrief Institute Data Core has refined search processes over the last 40 years, limiting some of the impact of these potential sources of error. The study is limited in that the control group may have been different at their presentation for threatened preterm labor, which is why the women did not get ACS in that group. We limited the control group to women who were also evaluated for threatened preterm labor in an attempt to try to match symptoms that might be related to underlying risk. We then controlled for factors different between the groups, such as diabetes and hypertension, that may have been reasons why some women received ACS and others did not. We were also limited in not capturing children who may have gotten care in a different health system. We do not believe that this percentage would be systematically different between case and controls, however. Our baseline estimate of population incidence of asthma of 10% was similar to our finding in the unexposed group of 11.6%. The rate in the ACS-exposed group was small at 12.6%. Our cohort, while large, was not powered to detect this small of a difference. It would take a total cohort size of >44,000 to have 80% power for this difference to be statistically significant.

Strengths of the study involve a large data set utilizing honest data brokers for a system-wide EMR. Additionally, we manually reviewed data on a subset of the records to ensure validity.

### Conclusions

In conclusion, babies born at term who were exposed to ACS may have increased rates of being in a lower growth percentile than those unexposed. However, rates of diagnoses such as asthma, developmental delay, and ADD were not different.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## AJOG at a Glance

**Why was this Study conducted?**

This study aimed to address the long-term outcomes of term born infants whose mothers received antenatal corticosteroids (ACS) for threatened preterm labor.

**Key Findings**

While term born babies who were exposed to ACS had no increased rates of diagnoses such as asthma, developmental delay, and attention deficit disorders in comparison to term babies not exposed to ACS; those exposed to ACS had increased risk of being in the lower growth percentile.

**What does this add to what is known?**

ACS exposure may increase rates of term born babies being in a lower childhood growth percentile than those unexposed.

**Table 1:**

Baseline maternal and neonatal characteristics of cohort.

| | Overall Cohort (N=3556) | ACS-exposed (N=629) | ACS not-exposed (N=2927) | P value |
|---|---|---|---|---|
| Maternal Characteristics | | | | |
| Age (years), mean (SD) | 26.6 ± 5.8 | 27.2 ± 5.9 | 36.5 ± 5.8 | 0.003 |
| Ethnicity | | | | |
| Hispanic or Latino | 244 (6.9%) | 43 (6.8%) | 201 (6.9%) | 0.841 |
| Not Hispanic or Latino | 3227 (90.8%) | 573 (91.1%) | 2654 (90.7%) | |
| Unknown | 85 (2.4%) | 13 (2.1%) | 72 (2.5%) | |
| Race | | | | |
| Black | 847 (23.8%) | 142 (22.6%) | 705 (24.1%) | 0.607 |
| White | 2493 (70.1%) | 445 (70.8%) | 2048 (70.0%) | |
| Other/Unknown | 216 (6.1%) | 42 (6.7%) | 174 (5.9%) | |
| Insurance | | | | |
| Medicaid/Government | 2208 (62.1%) | 387 (61.5%) | 1821 (62.2) | 0.785 |
| Private | 1296 (36.5%) | 231 (36.7%) | 1065 (36.4%) | |
| None | 52 (1.5%) | 11 (1.8%) | 41 (1.4%) | |
| Maternal Diabetes, yes | 112 (3.2%) | 30 (4.8%) | 82 (2.8%) | 0.010 |
| Maternal Hypertensive disorder, yes | 298 (8.4%) | 112 (19.4%) | 176 (6.0%) | <0.001 |
| EGA when received ACS or were evaluated for threatened preterm labor (weeks), mean (SD) * | 31.8 ± 4.5 | 31.4 ± 3.0 | 31.9 ± 4.8 | 0.01 |
| Weeks from exposure to delivery, mean (SD) * | 7.1 ± 4.6 | 7.2 ± 3.4 | 7.1 ± 4.8 | 0.62 |
| Child Characteristics, mean (SD) | | | | |
| Age (years) when data was pulled, n=3556 | 6.9 ± 1.1 | 7.0 ± 1.1 | 6.9 ± 1.1 | 0.617 |
| EGA at delivery (weeks) | 38.9 ± 1.1 | 38.5 ± 1.1 | 39.0 ± 1.1 | <0.001 |
| Birth length (cm), n=3112 | 50.5 ± 3.7 | 49.9 ± 3.8 | 50.7 ± 3.6 | <0.001 |
| Head circumference at birth (cm), n=3046 | 34.0 ± 2.9 | 33.5 ± 2.7 | 34.1 ± 3.0 | <0.001 |
| Birth weight (gram), n=3213 † | 3290.7 ± 496.7 | 3191.8 ± 602.5 | 3311.9 ± 467 | <0.001 |
| Small for Gestational Age (SGA) at birth, yes, n=3213 † | 618 (19.2%) | 137 (21.8%) | 481 (16.4%) | 0.005 |

* The gestational age for women that did not receive ACS at the time of evaluation for threatened preterm labor is provided. This is provided for descriptive purposes only and not considered as a covariate since it is not directly comparable between exposure groups.

† Small for gestational age (SGA) was used rather than birth weight as primary outcomes

ACS=antenatal corticosteroids; EGA=estimated gestational age; NA=not applicable

**Table 2:**

Long-term childhood outcomes

| Outcomes, yes | Overall cohort (N=3556) | ACS-exposed (N=629) | ACS not-exposed (N=2927) | P value |
|---|---|---|---|---|
| Asthma | 417 (11.7%) | 79 (12.6%) | 338 (11.6%) | 0.474 |
| ADD | 100 (2.8%) | 20 (3.2%) | 80 (2.7%) | 0.539 |
| Hypoxemia | 58 (1.6%) | 10 (1.6%) | 48 (1.6%) | 0.928 |
| Tachypnea | 38 (1.1%) | 7 (1.1%) | 31 (1.1%) | 0.905 |
| Wheezing diagnoses | 283 (8.0%) | 49 (7.8%) | 234 (8.0%) | 0.864 |
| Albuterol use | 800 (22.5%) | 139 (22.1%) | 661 (22.6%) | 0.792 |
| Bronchiolitis | 604 (17.0%) | 114 (18.1%) | 490 (16.7%) | 0.402 |
| Developmental delay | 236 (6.6%) | 51 (8.1%) | 185 (6.3%) | 0.102 |
| Diabetes | 4 (0.1%) | 1 (0.2%) | 3 (0.1%) | 0.541 |
| Number of childhood hospitalizations, mean (SD) | 0.2 ± 0.7 | 0.2 ± 0.1 | 0.2 ± 0.1 | 0.774 |
| BMI percentile | | (n = 198) | (n = 925) | |
| < 10%, yes | 52 (4.6%) | 11 (5.6%) | 41 (4.4%) | 0.495 |
| > 90%, yes | 331 (29.5%) | 57 (28.8%) | 274 (29.6 %) | 0.815 |
| Height/Length percentile | | (n = 170) | (n = 778) | |
| < 10%, yes | 123 (13.0%) | 26 (15.3%) | 97 (12.5%) | 0.321 |
| > 90%, yes | 145 (15.3%) | 20 (11.8%) | 125 (16.1%) | 0.158 |
| Weight percentile | | (n = 227) | (n = 1052) | |
| < 10%, yes | 106 (8.3%) | 31 (13.7%) | 75 (7.1 %) | 0.001 |
| > 90%, yes | 332 (26.0%) | 58 (25.6%) | 274 (26.1%) | 0.877 |

Data shown are n (%) unless otherwise noted. ACS= antenatal corticosteroids, ADD= attention deficit disorder, BMI= body mass index

Rates of diagnoses from electronic medical records.

**Table 3:**

Multivariate model for neonatal long-term outcomes

| Covariates | Asthma | Weight percentile < 10%, yes |
|---|---|---|
| Maternal age (years) | 0.97 (0.95, 0.98) | 0.97 (0.94, 1.01) |
| EGA at delivery (weeks) | 0.84 (0.76, 0.93) | 0.86 (0.70, 1.05) |
| Maternal diabetes of mother, yes | 1.65 (0.97, 2.82) | --- |
| Maternal hypertensive disorder of mother, yes | 0.98 (0.66, 1.45) | 0.66 (0.30, 1.45) |
| Small for Gestational Age (SGA) at birth, yes | 0.94 (0.71, 1.24) | 2.09 (1.30, 3.35) |
| Group, ACS-exposed | 1.05 (0.79, 1.39) | 2.00 (1.22, 3.25) |

Regression model controlled for all variables in the model. ACS= antenatal corticosteroids.

Results are given in odds ratio (95% confidence interval)