Antenatal corticosteroids beyond 34 weeks gestation: What do we do now?

Beena D. Kamath-Rayne, MD, MPH, Associate Professor of Pediatrics, Paul J. Rozance, MD, Associate Professor of Pediatrics, Robert L. Goldenberg, MD, Professor of Obstetrics/Gynecology, Alan H. Jobe, MD, PhD, Professor of Pediatrics

PII: S0002-9378(16)30362-3
DOI: 10.1016/j.ajog.2016.06.023
Reference: YMOB 11160


Received Date: 23 April 2016
Revised Date: 3 June 2016
Accepted Date: 13 June 2016


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Antenatal corticosteroids beyond 34 weeks gestation: What do we do now?

Beena D. KAMATH-RAYNE, MD, MPH
Associate Professor of Pediatrics
Perinatal Institute
Cincinnati Children’s Hospital Medical Center
Cincinnati, Ohio
Beena.Kamath-Rayne@cchmc.org

Paul J. ROZANCE, MD
Associate Professor of Pediatrics
Division of Neonatology
University of Colorado School of Medicine
Aurora, Colorado
Paul.Rozance@ucdenver.edu

Robert L. GOLDENBERG, MD
Professor of Obstetrics/Gynecology
Department of Obstetrics/Gynecology
Columbia University Medical Center
New York, New York
rlg88@cumc.columbia.edu

Alan H. JOBE, MD, PhD
Professor of Pediatrics
Perinatal Institute
Cincinnati Children’s Hospital Medical Center
Cincinnati, Ohio
Alan.Jobe@cchmc.org

Word Count: Abstract 426; Body 3806

Funding Source: None

Conflicts of Interest: Dr. Alan Jobe has a grant from the Bill and Melinda Gates Foundation to study corticosteroids for fetal maturation in monkey and sheep models. He is a collaborator on a grant from Glaxo-Smith-Kline to study betamethasone pharmacokinetics in maternal and fetal sheep. He is the Chair of the NICHD Global Network, and both he and Dr. Robert Goldenberg were co-investigators in the Antenatal Corticosteroid Trial (ACT) trial published in Lancet in 2015. The other authors have nothing to disclose.
Summary

We review the risks, benefits and challenges in the use of antenatal corticosteroids beyond 34 weeks gestation.

Short Title

Antenatal corticosteroids beyond 34 weeks
ABSTRACT

The practice of antenatal corticosteroid (ANCS) administration in pregnancies 24 to 34 weeks at risk of preterm delivery was adopted over 20 years after the first randomized clinical trial in humans. It is biologically plausible that ANCS in pregnancies beyond 34 weeks would reduce rates of respiratory morbidity and neonatal intensive care admission. Mostly guided by the results of a large multicenter randomized trial of ANCS in late preterm infants, the Antenatal Late Preterm Steroids Trial (ALPS) trial, the American Congress of Obstetricians and Gynecologists has released a practice advisory that “administration of betamethasone may be considered in women with a singleton pregnancy between 34 0/7 and 36 6/7 weeks gestation at imminent risk of preterm birth within 7 days.”\(^1\,^2\) However, many unanswered questions about the risks and benefits of antenatal corticosteroids in this population remain, and should be considered with the adoption of this treatment recommendation.

This review of the literature indicates that the greatest effect is in the reduction of transient tachypnea of the newborn, a mostly self-limited condition. This benefit must be weighed against unanticipated outcomes, such as neonatal hypoglycemia, and unknowns about long term neurodevelopmental follow-up and metabolic risks. Amelioration of respiratory morbidity in late preterm infants does not preclude these infants from having other complications related to prematurity that require intensive care. Other possible morbidities of prematurity may be magnified if these babies no longer have respiratory symptoms. Conversely, if these late preterm babies no longer exhibit respiratory symptoms and “look good,” they may be discharged before other morbidities of prematurity have resolved and be at risk for re-admission. Furthermore, it is also important to ensure that unintended consequences are avoided to achieve a minor benefit. Some of these consequences may include treatment with multiple steroid courses or “treatment creep” in women between 34 to <37 weeks who do not meet the
inclusion/exclusion criteria of the ALPS study, particularly when a high percentage of women do not receive ANCS within 7 days of delivery.

Finally, we feel that caution should be exercised before wide scale universal adoption of ANCS for pregnancies at risk of preterm birth between 34-<37 weeks, when it is unclear if there are long term effects. For a more balanced rationale for the decision to utilize ANCS treatment in pregnancies >34 weeks, we urge for ongoing research into the risks and benefits of ANCS in preterm infants overall, better prediction of preterm birth so that ANCS can be administered within the ideal time frame, and long term neurodevelopmental follow-up of the participants in the large randomized ALPS trial.

**Key Words:** antenatal corticosteroids, betamethasone, dexamethasone, hypoglycemia, late preterm infants, respiratory distress syndrome, transient tachypnea of the newborn
INTRODUCTION

Liggins and Howie published the first randomized controlled trial of antenatal corticosteroids (ANCS) in *Pediatrics* in 1972 demonstrating a reduction in respiratory distress syndrome (RDS) in infants < 32 weeks gestation from 69.6% to 11.8%. ³ Fourteen more randomized controlled trials were reported before 1995, but the use of ANCS to reduce neonatal morbidity after preterm birth remained about 20-40%, primarily because of concerns about adverse effects of ANCS on the fetal brain. ⁴,⁵ A 1995 meta-analysis demonstrated an approximately 50% reduction in RDS in infants whose mothers were treated with ANCS, with the best treatment to delivery interval of 24 hours to one week after ANCS treatment. ⁵ Sinclair then calculated a number-needed-to-treat with ANCS of 4 for preterm deliveries <31 weeks, and 15 for deliveries at 31-34 weeks, to prevent one case of RDS. ⁶ In 1995, over 20 years after the original randomized trial, a multidisciplinary National Institutes of Health panel concluded in a consensus statement that ANCS for fetal maturation reduced neonatal mortality, RDS, and intraventricular hemorrhage in preterm infants and should be used for pregnancies likely to deliver between 24 to 34 weeks gestation. ⁷,⁸

Until the recent release of the practice advisory in April 2016,¹ the most up-to-date guideline was the 2011 American Congress of Obstetricians and Gynecologists (ACOG) practice bulletin regarding ANCS, which recommended a single course of ANCS for pregnant women between 24 and 34 weeks gestation at risk of preterm delivery.⁹ However, contentious issues regarding the use of ANCS still remain. Should the treatment be extended to infants beyond 34 weeks, where the risks of RDS and other problems of prematurity are less significant? What do we know about the longer term effects of ANCS in the late preterm population?
With biological plausibility that ANCS administration would benefit older fetuses, some obstetricians have given corticosteroids outside this recommended gestational window.\textsuperscript{10} Therefore, it is instructive to analyze the various studies in which ANCS were given >34 weeks gestation, the clinical situations of use, and the neonatal outcomes. Given recent publications addressing some of these unanswered questions about ANCS treatment, we will review the evidence regarding ANCS use beyond 34 weeks gestation in different clinical scenarios, and possible long-term consequences.

### USE OF ANTENATAL CORTICOSTEROIDS BEYOND 34 WEEKS GESTATION

**Antenatal corticosteroids after immature fetal lung indices**

A retrospective cohort study by Kamath-Rayne et al. followed the different clinical management of women at or beyond 34 weeks gestation who had an amniocentesis for fetal lung maturity testing. One-hundred-and-two women whose fetal lung indices were immature were given ANCS prior to delivery. The ANCS-exposed infants (delivered at a mean gestation of 36 weeks) had higher rates of a composite adverse respiratory outcome, neonatal intensive care admission, hypoglycemia, and sepsis evaluation, compared to 76 infants who delivered expectantly (mean 38 weeks) after immature fetal lung indices, and a third group of 184 infants who delivered after mature fetal lung indices (mean 37 weeks).\textsuperscript{10} A second retrospective cohort study by Yinon et al. evaluated 83 infants of women with immature fetal lung indices between 34-37 weeks who subsequently received betamethasone treatment versus 84 infants whose mothers did not, based on provider preference.\textsuperscript{11} There were no differences in RDS, transient tachypnea of the newborn (TTN), hypoglycemia, admission to special care unit, or length of hospitalization between groups.\textsuperscript{11} The rates of respiratory support (continuous positive airway
pressure or oxygen supplementation) and a composite respiratory outcome (RDS, TTN or respiratory support) were lower in the treated group (8.4% vs 20%, p=0.03; and 8.4% and 21%, p=0.02, respectively). It is important to note for the Yinon study that the average gestational age at delivery in the ANCS-exposed infants was later (37 vs. 36 weeks) and the time between amniocentesis and delivery was slightly longer (5 days vs. 4.6 days) than the Kamath-Rayne study.\textsuperscript{10,11}

A 2015 survey of 312 obstetricians and maternal-fetal medicine specialists showed that 44% of respondents use ANCS in patients >34 weeks gestation. Many were using steroids in both late preterm and early term periods after immature fetal lung indices and waiting on the basis of the lung maturity test result and its expected rate of rise over time (Visconti et al., unpublished data). Indeed, in a study by Shanks, et al. ANCS administration after 34 weeks gestation was associated with a higher mean weekly increase in a fluorescence polarization fetal lung maturity test (TDx-FLM II) than was no treatment, although the study was stopped early due to difficulty in patient recruitment and insufficient power to examine neonatal outcomes.\textsuperscript{12}

\textit{Antenatal corticosteroids before elective Cesarean delivery at term}

Three studies have evaluated the use of ANCS before elective Cesarean delivery at term. The Antenatal Steroids for Term Elective Cesarean Section (ASTECS) study, by Stutchfield et al.,\textsuperscript{13} evaluated ANCS for 998 women who planned an elective Cesarean delivery at 37 weeks or beyond. The primary outcome was admission to the special care unit with respiratory distress. The authors described the study as a multicenter pragmatic randomized trial; it was not blinded, and the criteria for admission to the different levels of intensive care were not clearly defined. Despite these weaknesses in study design, admission to the special care unit for
respiratory distress decreased from 5.4% (24 patients) in the control group to 2.9% (11 patients) in the treatment group (p=0.02), and RDS was reduced between control and treatment groups (1.1% vs. 0.2%), which was not statistically significant. Despite a decrease in admissions for respiratory distress in the ANCS-exposed group, there were similar numbers of admissions to the special care nursery in both groups (26 in treatment group and 32 in control group), although the authors note that the level of intensive care was less in the treatment group (Table 1).13

A non-blinded randomized trial by Ahmed et al. analyzed the effect of two doses of antenatal dexamethasone given to a group of pregnant women at 37 weeks or beyond prior to elective Cesarean section (Table 1).14 While the rates of respiratory distress overall were decreased in the treatment group (7.9% vs. 23.2%, p<0.01), the decrease was primarily from transient tachypnea of the newborn (TTN, 7% vs. 19.6%).14 Similar to the Stutchfield et al. study, there were large absolute differences in rates of RDS (0.9% vs. 3.6%, p=0.40) and admission to the neonatal intensive care (NICU; 0.9% vs 6.3%, p=0.07) associated with ANCS that were not statistically significant. The duration of admission to NICU was shorter in the treatment group (1.1 days compared to 3.8 days, p<0.01).14

Finally, Nada et al. performed a randomized placebo-controlled trial of 3 doses of dexamethasone 48 hours prior to elective Cesarean section at 38 to <39 weeks gestation. In contrast to the other two studies, the treatment group had significantly decreased rates of admission to NICU overall. Similar to the Stutchfield et al. study, there was a significant decrease in NICU admission due to respiratory distress, likely mediated by the decrease in TTN in the treatment group compared with control (1.3% vs. 3.4%, p=0.01).

In summary, these three trials demonstrate a low incidence of respiratory-related adverse outcomes such as RDS after Cesarean section at term, and the greatest effect of ANCS exposure
in reduction of respiratory morbidity is related to TTN. While not statistically significant, all three trials show a directionally similar reduction in RDS and NICU admission.

**Antenatal corticosteroids in the late preterm period**

Older studies which included small numbers of infants >34 weeks did not show a benefit of ANCS. Crowley’s meta-analysis in 1995 included 29 cases of RDS in 886 infants >34 weeks, with no significant improvement in the incidence of RDS.\(^5\) Based on these numbers, Sinclair calculated a number-needed-to-treat of 145 to prevent one case of RDS.\(^6\) The Roberts and Dalziel meta-analysis included 189 infants treated between 35 to <37 weeks with the first dose of ANCS and showed no difference in rates of RDS.\(^15\) Since that meta-analysis was updated in 2010, further studies analyzing the use of ANCS in pregnancies >34 weeks are listed here. In 2010, Balci et al., published a prospective clinical trial of 100 women at 34 to 36 weeks gestation, half of whom were randomized to receive a single dose of betamethasone at least 24 hours prior to delivery. Rates of RDS with admission to NICU were reported to be 4% in the treatment group versus 16% in the control group (p=0.046, with odds ratio of 0.21 [0.04-1.08]). TTN was not discussed.

Porto et al. performed a randomized triple-blinded controlled trial of ANCS in Brazil that included 320 women at 34-36 weeks gestation at risk of imminent premature delivery who were randomized to a course of betamethasone versus placebo (Table 2).\(^16\) The average gestational age of both groups at delivery was the same. When comparing the treatment and control groups, there were no differences in rates of neonatal intensive care admission, respiratory morbidity, RDS, TTN, hypoglycemia or length of NICU stay.\(^16\)
A non-randomized prospective cohort study in Lebanon by Ramadan et al. compared the infants of women between 34 and <37 weeks at risk of imminent preterm delivery whose providers treated with antenatal betamethasone, to a group whose providers did not (Table 2). Of note, the control group had a higher number of babies 36 to <37 weeks, and the treatment group had higher numbers of babies 34 to < 35 weeks. Similar to the Porto et al. study, they noted no differences in rates of RDS, TTN, respiratory morbidity, neonatal intensive care admission, or NICU stay. As opposed to the Porto et al. study, however, they detected statistically increased rates of hypoglycemia and suspected sepsis in the treated group.

In February, 2016, the results of the large randomized controlled double-blind Antenatal Late Preterm Steroids Trial (ALPS) were published. Women with a singleton pregnancy and without previous exposure to ANCS who were at high risk of imminent delivery in the late preterm period (34 to 36 weeks 6 days) were randomized to betamethasone 12 mg for 2 doses given 24 hours apart versus placebo. High risk of imminent delivery was strictly defined as preterm labor with intact membranes and at least 3 cm dilation or 75% cervical effacement, or spontaneous rupture of membranes. There was no statistical difference in rates of RDS, the need for mechanical ventilation or NICU admission between groups (Table 2), although these were notably higher than rates seen in term infants (Table 1). There was a statistical difference in the primary outcome, a composite endpoint occurring within 72 hours of birth and consisting of one 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, or mechanical ventilation. Rates of the primary outcome were 11.6% in the treatment group compared to 14.4% in the control group (relative risk 0.80 (95% CI 0.66-0.97; p=0.02).
was also a decreased need for surfactant in the ANCS group (1.8% vs 3.1%, \( p=0.03 \)). An unanticipated finding was an increased incidence of hypoglycemia, defined as a glucose level <40 mg/dL, in the ANCS group compared to the control group (24.0% vs. 15.0%, relative risk 1.60; 95% CI 1.37-1.87; \( p<0.01 \)). While there was no discussion of number of blood glucose measurement, the nadir of these levels, maternal blood glucoses, nor interventions required for hypoglycemia, the infants with hypoglycemia were discharged an average of 2 days earlier than those without hypoglycemia, suggesting that the condition was “self-limiting.” The composite outcome of severe respiratory morbidity (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 24 continuous hours, ECMO or mechanical ventilation, stillbirth, or neonatal death within 72 hours after delivery) was lower in the treatment group compared to the control group (8.1% vs 12.1%; relative risk 0.67; 95% CI 0.53-0.84; \( p<0.01 \)), and the number-needed-to treat to prevent one case of the primary outcome was 35. No long-term follow-up data were presented.

The Society of Maternal-Fetal Medicine and ACOG have now recommended guidelines to adopt and implement the findings of the ALPS study into clinical practice. The recommendations include an adherence to the criteria for preterm labor in order to decrease the potential risk for overtreatment of women who would ultimately deliver at term. They acknowledge a lack of long term neonatal outcome data and recommend standard guidelines for the assessment of monitoring of neonatal hypoglycemia in late preterm infants.

**Challenges and consequences to antenatal corticosteroid use in late preterm infants**

Neonatologists have long struggled to understand the complex relationship between glucocorticoids and neurodevelopmental impairment. Glucocorticoids can have beneficial
effects on the developing brain.\textsuperscript{19} However, the gestational age at the time of the exposure, the duration of the exposure, the pharmacodynamics of the steroid, and genetic variation in glucocorticoid receptors in the brain all may modulate how the effects are manifested in the short and long term.\textsuperscript{19,23} There are steroid treatments with betamethasone and dexamethasone that are effective for the preterm infant, but the minimal doses have not been adequately evaluated.\textsuperscript{24,25}

While a single course of ANCS appears to improve neurodevelopmental outcomes in infants born \textless{}34 weeks gestation,\textsuperscript{26} little is known about the long-term effects of exposure to ANCS after 34 weeks gestation. This time period is critical for brain development, as at 34 weeks, the brain weight is only 65\% of the term brain, and gyral and sulcal formation are still incomplete.\textsuperscript{27} Between 34 and 40 weeks gestation, cortical volume increases by 50\% and 25\% of the cerebellar development occurs.\textsuperscript{27} Stutchfield et al. performed a follow-up assessment to the ASTECS trial of betamethasone before an elective Cesarean section at term.\textsuperscript{28} 93\% of the original cohort were able to be contacted, but only 51\% completed the questionnaires that served as the basis for the assessment.\textsuperscript{28} While there were no differences in behavior and health for the subjects at 8-15 years of age, a higher incidence of being in the lowest quarter of academic ability was noted in the betamethasone group (17.7\% vs 8.5\%).\textsuperscript{28}

Several studies have examined the metabolic and hormonal effects of ANCS administered in the late preterm period. Hypoglycemia was noted in late preterm infants whose mothers were treated with ANCS in several studies.\textsuperscript{2,10,17} In a retrospective cohort study of 6,675 preterm deliveries at 32 to 37 weeks at a single university hospital, the odds ratio of hypoglycemia in corticosteroid-exposed infants, after adjustment of gestational age, was 1.60 (95\% CI 1.24-2.07). The hypoglycemia was increased in infants whose mothers had pre-gestational diabetes (adjusted OR 5.65 [95\% CI 3.84-8.33]).\textsuperscript{29} However, there were no
statistically significant differences between groups when stratified by gestational age. A limitation of the study was the lack of maternal blood glucose levels. Sifianou et al. analyzed cord blood in a convenience sample of 32 singleton newborns >35 weeks whose mothers received a single 12 mg dose of betamethasone approximately 24 hours prior to planned Cesarean delivery. This group was compared to 44 babies of comparable gestational age, sex, and nutritional status who were not exposed to ANCS. None of the mothers had pre-gestational or gestational diabetes. Cord blood levels of C-peptide and glucose were higher in ANCS exposed fetuses, indicating these fetuses were hyperinsulinemic and thus at higher risk for neonatal hypoglycemia.

Finally, ANCS therapy in preterm infants may lead to cardiovascular and metabolic health problems in later life, although the reports, mostly derived from observational studies, are conflicting. For example, a cohort of 210 preterm survivors followed until age 14 years had higher systolic and diastolic blood pressures in adolescence, which could lead to clinical hypertension later in life. Potential mechanisms responsible for this observation have been identified in animal studies. A different cohort of 209 term born children who were exposed to ANCS in approximately the 30th week of gestation had significantly increased cortisol reactivity to psychosocial stress when evaluated at 6 to 11 years of age, suggesting longer term effects of ANCS on the hypothalamus-pituitary-adrenal (HPA) axis than previously thought. However, it is important to note that there are no data on long term cardiovascular or metabolic data on late preterm or term infants.

**Challenges for administration of antenatal corticosteroids**
There are clear benefits to administration of ANCS in preterm gestation when delivery occurs 24 hours to 7 days after treatment.\textsuperscript{15} However, ensuring that ANCS are given at the correct time, without adequate methods to predict the timing of preterm birth, is an ongoing challenge. Many perinatal collaboratives use treatment with ANCS as a marker of quality, and rates of ANCS have increased to about 90\% for deliveries 24 to 34 weeks.\textsuperscript{35,36} However, of concern, there has been a subsequent increase in suboptimal treatment (less than 24 hours or more than 7 days before delivery) and questionably appropriate treatment (35 weeks or greater exposed to ANCS). In all live births in Nova Scotia from 1998-2012, the rates of suboptimal treatment were 34\% (odds ratio 6.7, 95\% CI 3.9-11.6) and questionably appropriate treatment of 1.7\% (odds ratio 7.5, 95\% CI 4.9-11.3).\textsuperscript{37} In fact, in 2012, more than half the newborns whose mothers received ANCS were born at 35 weeks gestation, and thus were unnecessarily exposed.\textsuperscript{37} Another study demonstrated that of 692 women receiving ANCS at a single institution, 35.7\% delivered at or >34 weeks gestation, and 17.9\% remained pregnant beyond a week after ANCS and were still <34 weeks.\textsuperscript{38} A rescue dose of steroids is often used in these situations; however, multiple courses of ANCS are not recommended due to poor fetal head growth and increased risk of neurodevelopmental impairment by 5 years.\textsuperscript{39-41} To fully implement ANCS to the greatest benefit of the preterm pregnancies at risk of imminent delivery, improved methods of preterm birth prediction are needed.\textsuperscript{42,43} Furthermore, if ANCS treatment is extended from 34 to <37 weeks and many of these fetuses deliver at term, the effects are unknown.

CONCLUSIONS

Antenatal corticosteroids are an important evidence-based practice for reducing mortality, and decreasing rates of RDS, intraventricular hemorrhage, and necrotizing enterocolitis in
premature infants, and the benefits of treatment in the <34 week gestation time period clearly outweigh the risks. At early gestational ages, ANCS may prevent significant short term neonatal morbidity that could greatly impact future neurodevelopmental outcome. In the late preterm and term period, these effects are much less clear. We felt that it was important to separate the situations in which ANCS are utilized: giving steroids prior to a planned Cesarean section at term without labor may have a different risk/benefit ratio than ANCS given to a woman at risk of delivery in the late preterm period.

For ANCS given prior to an elective Cesarean section at term, the three studies described showed decreased rates of NICU admission for respiratory morbidity, likely related to decreased incidence of TTN. However, there was no decrease in rates of RDS, nor in NICU admission overall, except in the Nada et al. study. Thus, in the term period, the greatest effect of ANCS is a decrease in rates of TTN, normally a self-limiting process. We must weigh this relatively small benefit with a lack of follow-up information for term infants exposed to ANCS, with a concern for longer term effects on academic performance in the ASTECS follow-up.

Even before the publication of the ALPS trial for ANCS use >34 weeks, there has been treatment creep of this practice outside of current practice recommendations. While the ALPS trial supports improvements in respiratory morbidity after infants are exposed during late preterm gestation, it is important to note that there were no significant differences in rates of RDS nor NICU admission. The rationale for how the authors derived their primary composite outcome measure and whether this composite outcome is of clinical significance is unclear. Most babies that had the primary composite outcome had respiratory morbidity related to TTN. Given the predisposition seen treatment creep, it is of concern that obstetricians may not adhere to the
inclusion/exclusion criteria of the ALPS study, and more late preterm infants will be exposed to ANCS, when we do not fully understand the long term implications.

An unintended consequence of using ANCS to improve respiratory symptoms in late preterm infants is that it may unmask other morbidities, such as hypoglycemia. It should be noted that the risk of hypoglycemia in the late preterm infants in the ALPS study was higher than the benefit derived from decreased respiratory morbidity. While the authors speculate that the hypoglycemia was a mild and self-limited condition, the nadir of the infants’ blood glucose levels and treatments have not been reported. We presented one explanation for the hypoglycemia, a transient neonatal hyperinsulinism related to elevated maternal blood glucose levels. Another possible explanation is that the infants who were not exposed to ANCS were indeed sicker, as demonstrated by their increased incidence of respiratory symptoms, need for resuscitation, and longer duration of NICU stay. These sicker infants were likely admitted to the NICU and started on intravenous fluids, thus preventing possible hypoglycemia.

While the hypoglycemia appears to have been self-limiting, the longer term effects of the hypoglycemia in conjunction with ANCS exposure are unknown. While RDS in the late preterm and term period can be a serious condition, it is not associated with poor neurodevelopmental outcome. On the other hand, while the critical threshold glucose concentration below which neurological injury occurs has not been identified, significant hypoglycemia has been associated with poor outcomes in moderately born preterm infants (32-36 weeks). While the incidence of respiratory morbidity of late preterm infants antenatally exposed to ANCS is slightly decreased, rates of NICU admission were not, and it may just be that we are trading one morbidity for another. Further details on the hypoglycemia and a cost analysis of the use of NICU resources would be helpful to further elucidate these issues.
While ANCS exposure may decrease respiratory symptoms, these babies still require close observation for other preterm morbidities including hypoglycemia, jaundice, hypothermia, and feeding difficulties.\textsuperscript{49} Providers should not be fooled into thinking these infants “look good” and discharge them earlier than recommended guidelines, which could increase rates of later morbidity or re-admission. In addition, long term follow-up data from the ALPS trial would be invaluable to understanding how ANCS exposure (with and without hypoglycemia) affects the late preterm brain.

With so many unknowns, the question facing all of us is whether the benefits of less short term, potentially self-limited, respiratory morbidity outweighs unclear and unknown longer term neurodevelopmental and metabolic risks for the late preterm or term infant exposed to ANCS. When the rapid development of recommendations to treat with ANCS in the late preterm period is juxtaposed to the over 20 years it took to adopt ANCS into obstetric practice in the first place, we strongly urge for a more thoughtful and balanced approach, and a greater understanding of the long term outcomes before quickly changing clinical practice when so many unknowns still exist.

WORKS CITED


### Table 1: Studies comparing the use of Antenatal Corticosteroids for Elective Cesarean Delivery at Term

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment (N)</th>
<th>Control (N)</th>
<th>Antenatal Corticosteroid Used</th>
<th>Mortality</th>
<th>Neonatal Intensive Care Admission (NICU)</th>
<th>Respiratory Distress Syndrome (RDS)</th>
<th>Transient Tachypnea of Newborn (TTN)</th>
<th>Respiratory morbidity</th>
<th>Hypoglycemia</th>
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<tbody>
<tr>
<td>Stutchfield et al. (2005)</td>
<td>373</td>
<td>446</td>
<td>Bethamethasone 12 mg x 2 doses, 24 hours apart</td>
<td>None reported</td>
<td>6.9% vs. 7.1% (NS)*</td>
<td>0.2% vs. 1.1% (RR 0.21, 0.03-1.32)</td>
<td>2.1% vs. 4.0% (RR 0.54, 0.26-1.12)</td>
<td>Defined as respiratory distress with admission to NICU 2.4% vs 5.1% (RR 0.46, 0.23-0.93)</td>
<td>Did not report</td>
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<tr>
<td>Ahmed, et al. (2015)</td>
<td>228</td>
<td>224</td>
<td>Dexamethasone 12 mg x 2 doses, 24 hours apart</td>
<td>None in either group</td>
<td>0.9% vs 6.3% (p=0.07)</td>
<td>0.9% vs 3.6% (p=0.4)</td>
<td>7% vs. 19.6% (p&lt;0.01)</td>
<td>“Respiratory distress morbidity” 7.9% vs. 23.2% (p&lt;0.01)</td>
<td>Did not report</td>
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<tr>
<td>Nada, et al. (2015)</td>
<td>616</td>
<td>611</td>
<td>Dexamethasone 8 mg, 12 hours apart x 4 doses, 48 hours prior to delivery</td>
<td>0.2% vs 0.3% (p=0.99)</td>
<td>3.1% vs 6.7% (p&lt;0.01)</td>
<td>0.6% vs. 1.6% (p=0.10)</td>
<td>1.3% vs. 3.4% (p=0.01)</td>
<td>Defined as NICU admission with respiratory morbidity 1.6% vs 3.9% (p=0.01)</td>
<td>Did not report</td>
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*Not significant, no p-value reported

RR= relative risk
Table 2: Studies comparing the use of Antenatal Corticosteroids for Late Preterm Infants at Risk of Preterm Delivery

<table>
<thead>
<tr>
<th>Authors</th>
<th>Treatment (N)</th>
<th>Control (N)</th>
<th>Antenatal Corticosteroid Used</th>
<th>Mortality</th>
<th>Neonatal Intensive Care Admission</th>
<th>Respiratory Distress Syndrome (RDS)</th>
<th>Transient Tachyypnea of Newborn (TTN)</th>
<th>Respiratory morbidity</th>
<th>Hypoglycemia</th>
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<td>Balci, et al. (2010)</td>
<td>50</td>
<td>50</td>
<td>Betamethasone 12 mg x 1 dose 24 hours prior to delivery</td>
<td>None reported</td>
<td>Only reported as RDS with admission to NICU</td>
<td>4% vs 16% (p=0.046)</td>
<td>Did not report</td>
<td>Did not report</td>
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<td>Porto, et al. (2011)</td>
<td>143</td>
<td>130</td>
<td>Betamethasone 12 mg x 2 doses, 24 hours apart</td>
<td>0 vs 2% (NS)*</td>
<td>33% vs 33% (NS)*</td>
<td>1% vs. 1% (p=0.54)</td>
<td>24% vs 22% (p=0.77)</td>
<td>25% vs 23% (p=0.69)</td>
<td>11% vs 7% (NS)*</td>
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<td>Ramadan et al. (2016)</td>
<td>74</td>
<td>221</td>
<td>Betamethasone 12 mg x 2 doses, 24 hours apart</td>
<td>0 vs 1% (NS)*</td>
<td>27% vs 19% (p=0.14)</td>
<td>8.1% vs. 6.8% (p=0.70)</td>
<td>8.1% vs. 6.8% (p=0.70)</td>
<td>17.6% vs 15.4% (p=0.66)</td>
<td>20.3% vs 10.9% (p=0.04)</td>
</tr>
<tr>
<td>Gyamfi-Bannerman (2016)</td>
<td>1427</td>
<td>1400</td>
<td>Betamethasone 12 mg x 2 doses, 24 hours apart</td>
<td>0.1% vs 0 (p=0.50)</td>
<td>41.8% vs 44.9% (p=0.09)</td>
<td>5.5 vs. 6.4% (p=0.36)</td>
<td>6.7% vs. 9.9% (p=0.01)</td>
<td>11.6% vs. 14.4% (p=0.02)</td>
<td>24.0% vs 15.0% (p&lt;0.01)</td>
</tr>
</tbody>
</table>

*NS=not significant, no p-value reported

1Primary outcome for this study was defined by any of the following occurrences within 72 hours after birth: Continuous positive airway pressure 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 extracorporeal membrane oxygenation.