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Antenatal Steroids For Late Preterm Pregnancies

Obstetric Consensus Conference

Shani Delaney, MD

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INTRODUCTION

Antenatal corticosteroids have been widely used in practice for pregnancies at risk for early preterm delivery. Historically, their use has been confined to pregnancies at less than 34 weeks gestation due to lack of data to support use beyond 34 weeks, as well as neonatal survival of late preterm infants closely approaching the survival of term infants^{1,2,3}. The late preterm period is defined as 34 weeks 0 days, through 36 week 6 days; with 8% of all deliveries occurring during this time period⁴. More recent literature has demonstrated that while overall survival in the late preterm period is within 1% of survival of term neonates, there are increased morbidities and long term complications of late preterm infants^{5,6,7}.

The National Institute of Health and Human Development (NICHD), in cooperation with the Maternal-Fetal Medicine Units Network (MFMU), recently published a randomized controlled trial, *Antenatal Betamethasone for Women at Risk for Late Preterm Delivery*, referred to as the “ALPS Trial”, evaluating the use of antenatal corticosteroids in late preterm pregnancies⁸. The Society of Fetal Medicine (SMFM) shortly thereafter published implementation guidelines supporting the NICHD/MFMU trial’s findings⁹.

The purpose of this consensus conference is to review the NICHD/MFMU trial results, and how we recommend implementation of this new data into our clinical practice at the University of Washington.

BACKGROUND LITERATURE – REVIEW OF THE ALPS TRIAL

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery, referred to as the “ALPS Trial”, is an NICHD/MFMU randomized controlled trial conducted at 17 university-based medical centers between 2010-2015. Women with a singleton pregnancy at 34+0 – 36+5 with a high probability of preterm delivery in the late preterm period were enrolled; with 2831 women undergoing randomization to receive the standard dosing of betamethasone 12mg IM q 24 hours x 2 doses or placebo. After randomization, patients were treated clinically according to local practice.

Inclusion criteria for what constituted “at risk for delivery in the late preterm period”:

- preterm labor with intact membranes: at least 3cm cervical dilation or 75% cervical effacement
- spontaneous preterm premature rupture of membranes (PPROM)
- planned delivery in the next 24 hours – 7 days due to medical or obstetric complications (i.e. oligohydramnios, growth restriction, preeclampsia, bleeding previa, abruption, prior myomectomy or classical hysterotomy)

Exclusion criteria:

- likely to deliver within 12 hours
- ruptured membranes with more than 6 contractions per hour or cervical dilation >3cm (unless oxytocin was withheld for at least 12 hours)
- had received a previous course of antenatal steroids
- pre-gestational diabetes
- contraindication to corticosteroids
- fetal anomalies
- twins reduced to singleton at >14 weeks
- maternal chronic steroid therapy

The primary outcome was a composite end point describing the need for neonatal respiratory support within 72 hours after birth. It consisted of one or more of the following:

- Continuous positive airway pressure (CPAP) or high flow nasal cannula (HFNC) >1L/min for at least 2 consecutive hours
- Supplemental oxygen with a FiO₂ of at least 0.30 for at least 4 consecutive hours
- Extracorporeal membrane oxygenation (ECMO)
- Mechanical ventilation
- Stillbirth or neonatal death within 72 hours after delivery

Secondary neonatal respiratory outcomes included a composite of severe respiratory complications: CPAP or HFNC oxygen for ≥ 12 hours, supplemental oxygen (O₂) at FiO₂ of at least 0.30 for ≥ 24 hours, ECMO or mechanical ventilation, stillbirth or neonatal death within 72 hours, respiratory distress syndrome, transient tachypnea of the newborn, apnea, bronchopulmonary dysplasia, surfactant administration, need for resuscitation at birth, hypoglycemia, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage, neonatal sepsis, pneumonia, or death before discharge.

Other secondary neonatal outcomes included hypoglycemia (<40mg/dL), median time to first feeding, feeding difficulties, hyperbilirubinemia, hypothermia, admission to intermediate care nursery or NICU, and length of hospital stay.

Maternal secondary outcomes included chorioamnionitis, endometritis, delivery before completion of the steroid course, and length of hospitalization

The study found a significant decrease in the primary outcome of need for respiratory support within the first 72 hours after birth (14.4% in the placebo group vs 11.6% in the betamethasone group, RR 0.80, 95% CI 0.66 – 0.97, p =0.02). There was also a significant decrease in the secondary outcome of severe respiratory morbidity (12.1% in the placebo group vs 8.1% in the betamethasone group, RR 0.67, 95% CI 0.53-0.84, p <0.001). In subgroup analysis, the decrease in primary respiratory outcome was not seen for pregnancies ≥ 36+0 (7.1% in the placebo group vs 7.1% in the betamethasone group, RR 1.0, 95% CI 0.64 – 1.6, p =0.27). Time to first feeding was decreased, and duration of NICU stay ≥3 days was less frequent in the betamethasone group. There was an increase in the frequency of neonatal hypoglycemia (15.0% in the placebo group vs 24.0% in the betamethasone group, RR 1.60, 95% CI 1.37-1.87, p <0.001). There were no differences in maternal outcomes.

DISCUSSION

The ALPS trial is the largest available randomized controlled trial evaluating the benefits and harms of antenatal corticosteroids in the late preterm period. Two small randomized controlled trials have been published prior to the ALPS trial regarding antenatal steroids in the late preterm period^{10,11}. However, these two studies are less informative than hoped for as they were underpowered to detect their primary outcome, had substantial loss to follow up as well as less rigorous methodology than ALPS. The largest similar study prior to the ALPS trial was the ASTECS Trial: Antenatal Steroids for Term Elective Cesarean Trial¹². ASTECS included 998 women undergoing scheduled cesarean section at term, randomized to pre-delivery betamethasone or placebo. The betamethasone group in the ASTECS trial had lower rates of NICU admissions due to respiratory complications as compared to placebo (RR 0.46, 95% CI 0.2-0.93). Due to the ASTECS Trial, it is standard of care in the United Kingdom to give pre-delivery betamethasone to patients undergoing scheduled cesarean delivery at term.

The findings of the ALPS trial are very similar to other studies regarding antenatal corticosteroids administered to patients at risk of early preterm delivery < 34 weeks gestation¹. Positive attributes of ALPS include the large sample size, a study cohort that is generalizable to the US population and the rigorous study design. The ALPS Trial does not provide long term childhood outcomes data, however existing data does not suggest an increased risk of long-term adverse effects in preterm newborns who have received a single course of antenatal steroids^{13,14}.

Given the findings of the ALPS Trial, SMFM supports administration of antenatal corticosteroids for patients at risk of late preterm delivery, with a few considerations.

ADDITIONAL CLINICAL MANAGEMENT

The ALPS Trial did not attempt to change clinical management, other than to administer antenatal corticosteroids. Thus, SMFM recommends that use of betamethasone in this time period should not involve measures to prolong pregnancy, whereas otherwise delivery would be indicated (i.e. Tocolysis, expectant management of severe preeclampsia). We agreed that the decision to administer betamethasone in the late preterm period should be made judiciously and independently of the decision for expectant management or delivery of high risk issues. Once the decision for expectant management has been made in the late preterm period, then antenatal corticosteroids should be considered at that time. (This includes the scenario of counseling regarding expectant management of PPROM beyond 34 weeks gestation, with guidance per the June 2016 UWMC Consensus Conference publication¹⁵. The decision regarding candidacy for expectant management of PPROM beyond 34 weeks should be made first and independently from the decision to give antenatal corticosteroids beyond 34 weeks.)

PRETERM LABOR DEFINITION > 34 WEEKS

SMFM highlights the strict preterm labor entry criteria for ALPS: at least 3cm cervical dilation or 75% effacement for preterm labor. We support the study's strict criteria for the definition of preterm labor beyond 34 weeks, in order to reduce the risk of over-treatment of women who will ultimately deliver at term.

Additionally, SMFM implementation guidelines include administration of antenatal corticosteroids in the late preterm period only for women who met the following study entry criteria: singletons, no prior receipt of antenatal corticosteroids at <34 weeks (i.e., this should not be used as rescue corticosteroids), absence of pre-

gestational diabetes or fetal anomalies, and patients with scheduled deliveries at 36+6 or less. We will review these criteria individually below, as they apply to our practice at UWMC.

PRIOR RECEIPT OF ANTENATAL CORTICOSTEROIDS AT <34 WEEKS GESTATION

We feel comfortable supporting SMFM implementation guidelines to avoid the administration of “rescue steroids” in the late preterm period, given to women who have already received betamethasone previously in pregnancy. While we have excellent data regarding rescue steroid use at <34 weeks gestation^{16,17,18}, the potential risks of repeat corticosteroid administration in the late preterm period to those fetuses who have already been exposed earlier in pregnancy, remains unknown. At this time, we would be consistent with ALPS Trial entry criteria to exclude women who have already received antenatal corticosteroids earlier in pregnancy.

MULTIPLE GESTATIONS

While the ALPS Trial excluded multiple gestations, current standard of care practice includes use of betamethasone for multiple gestations at risk for early preterm delivery < 34 weeks. The 2006 Cochrane Review on antenatal corticosteroids contains a subgroup analysis including multiple gestations. All of the of relative risk reductions for multiple gestation neonatal morbidities were similar to the risk reductions observed in singleton gestations; although, the multiple gestation numbers were small, which meant the confidence intervals were wide and crossed one¹. We support extension of the ALPS Trial criteria at the University of Washington, to include multiple gestations as candidates to receive antenatal corticosteroids in the late preterm period.

PRE-GESTATIONAL DIABETES OR A2 GESTATIONAL DIABETES

In regards to patients with pre-gestational diabetes or A2 gestational diabetes, there is certainly room for individualized care and decision making. While the ALPS trial excluded women with pre-gestational diabetes, clinically some women with pre-gestational diabetes may be on fewer medications than a patient who has the diagnoses of A2 gestational diabetes. Thus, given the respiratory benefit demonstrated in the ALPS trial, and the known increased risk of pulmonary immaturity for infants of diabetic mothers^{19,20}, we feel that the neonates of pre-gestational diabetic women may benefit from administration of antenatal corticosteroids in the late preterm period. We leave it to the clinician’s discretion on Labor and Delivery to evaluate the overall clinical scenario and weight the risks and benefits regarding an individualized clinical plan to administer late preterm corticosteroids to pre-gestational or A2 gestational diabetics.

FETAL ANOMALIES

The ALPS Trial excluded women with known fetal anomalies, in order to reduce bias in neonatal outcomes that could be effected by the anomaly itself. Given the positive effects seen for normal fetuses in the ALPS Trial, we recommend extension of use to include pregnancies with known fetal anomalies.

SCHEDULED CESAREAN SECTION AT 37+0 WEEKS GESTATION

The ALPS trial included women undergoing planned deliveries no later than 36+6. For those women with scheduled cesarean deliveries at 37+0 due to indications such as placenta previa, prior myomectomy, prior classical hysterotomy, or other medical and obstetric complications of pregnancy, we feel that extending the ALPS Trial inclusion criteria to 37+0 for cesarean deliveries is reasonable, and may be supported additionally by data from the ASTECS Trial. Administration of antenatal corticosteroids should not occur for any pregnancy with a planned delivery beyond 37+0 week gestational age at this time at UWMC. For those *cesarean* deliveries

planned at 37+0, we recommend administration of scheduled antenatal betamethasone closer to 36+0, in order to avoid transient maternal hyperglycemia at delivery and the potential to further increase neonatal hypoglycemia after birth. We do not recommend administration of late preterm corticosteroids to patients undergoing *induction of labor* at 37+0, as these patients will likely deliver beyond 37+0, in addition to gaining the known neonatal respiratory benefits of undergoing a trial of labor^{21,22,23}.

NEONATAL HYPOGLYCEMIA

The only increased morbidity detected in the ALPS trial, was an increase in neonatal hypoglycemia in the betamethasone group. While there was an observed increase from 15% in the placebo group to 24% in the treatment group, there were no reported adverse outcomes due to hypoglycemia in any newborns in the trial. The potential for increased neonatal hypoglycemia can be managed by routine newborn glucose testing, as recommended for all preterm infants by the Committee on Fetus and Newborn of the American Academy of Pediatrics²⁴. Neonatology should be updated regarding recent betamethasone administration at delivery, similar to any other pertinent maternal medications which may affect care of the newborn.

36-WEEK SUBGROUP ANALYSIS

In the supplementary material to the ALPS trial, the authors performed subgroup analyses evaluating both the primary composite respiratory outcome as well as the secondary severe composite respiratory outcome stratified by gestational age. Both the primary and secondary respiratory outcomes remained significant only for those patients recruited at <36 week 0 days. This is certainly plausible from a biological standpoint given continuing maturation of fetal type 2 surfactant-producing pneumocytes with each week of advancing gestation. This suggests that neonates ≥36+0 weeks gestation do not gain the same benefit as those patients receiving late preterm corticosteroids between 34+0 – 35+6 weeks gestation.

SUMMARY OF RECOMMENDATIONS

- 1) We support judicious administration of antenatal corticosteroids to women between 34+0 and 36+5 who are at risk of late preterm delivery <37 weeks. Treatment should be 2 doses of betamethasone 12mg IM 24 hours apart. Treatment should be initiated no later than 36+5, so that completion of steroids occurs by 37+0. The patients most likely to benefit from late preterm corticosteroids are those patients < 36+0 weeks.
- 2) The decision to expectantly manage a high risk pregnancy beyond 34 weeks should be made initially and independently from the decision to administer corticosteroids in the late preterm period. Once the decision has been made to expectantly manage a pregnancy beyond 34 weeks, and the risk of delivery in the late preterm period remains high, then administration of betamethasone should be pursued.
- 3) Preterm labor between 34+0 and 36+5 should adhere to the ALPS Trial entry preterm labor criteria to avoid over-treatment of women who would eventually deliver at term: at least 3cm cervical dilation or 75% effacement for preterm labor. For cases of PPROM, women should have no more than 6 contractions per hour.
- 4) We support the use of indicated late preterm corticosteroids for multiple gestations.
- 5) We support the use of indicated late preterm corticosteroids for pregnancies with fetal anomalies.
- 6) Clinical judgement should be used prior to administering corticosteroids to pre-gestational diabetics, or A2 gestational diabetics.
- 7) Late preterm corticosteroids should not be used as “rescue” steroids at this time, until further research can be provided on the safety of repeat late preterm antenatal corticosteroids in those patients who have already received a previous dose at <34 weeks gestational age.
- 8) For women with scheduled *cesarean* deliveries at 37+0 due to medical and/or obstetrical complications of pregnancy, we recommend administration of antenatal corticosteroids approximately one week prior to the scheduled delivery date, in order to avoid peak maternal hyperglycemia at delivery. Steroids should not be given to scheduled 37+0 inductions, nor any patient with a planned delivery beyond 37+0 weeks gestation.
- 9) At the time of delivery, the pediatric care team should be updated on all recent maternal medications, particularly recent betamethasone use >34 weeks, given the increased risk of neonatal hypoglycemia in women receiving antenatal corticosteroids in the late preterm period.

DISCLAIMER

This consensus document is to be used as a guideline for practice management. It is generated by expert review from the Departments of Obstetrics and Gynecology & Neonatology. If clinical judgment by providers involves deviation from these recommendations, then appropriate documentation regarding that decision-making should be available in the patient chart.

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