RCT
Potential PURL Review Form
PURL Jam Version
Version #11 October 29, 2009

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, Rouse DJ, McKenna DS, Clark EA, Thorp JM Jr, Chien EK, Peaceman AM, Gibbs RS, Swamy GK, Norton ME, Casey BM, Caritis SN, Tolosa JE, Sorokin Y, VanDorsten JP, Jain L; NICHD Maternal–Fetal Medicine Units Network. Antenatal Betamethasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016 Apr 7;374(14):1311-20.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/26842679
3. First date published study available to readers	04/07/2016
4. PubMed ID	26842679
5. Nominated By	Other: Kate Endicott
6. Institutional Affiliation of Nominator	Other:
7. Date Nominated	04/16/16
8. Identified Through	Other: TOC
9. PURLS Editor Reviewing Nominated Potential PURL	Other:
10. Nomination Decision Date	04/21/16
11. Potential PURL Review Form (PPRF) Type	

12. Other comments, materials or discussion

13. Assigned Potential PURL Reviewer

14. Reviewer Affiliation Other:

15. Date Review Due 07/07/16

16. Abstract

BACKGROUND:
Infants who are born at 34 to 36 weeks of gestation (late preterm) are at greater risk for adverse respiratory and other outcomes than those born at 37 weeks of gestation or later. It is not known whether betamethasone administered to women at risk for late preterm delivery decreases the risks of neonatal morbidities.
METHODS:
We conducted a multicenter, randomized trial involving women with a singleton pregnancy at 34 weeks 0 days to 36 weeks 5 days of gestation who were at high risk for delivery during the late preterm period (up to 36 weeks 6 days). The participants were assigned to receive two injections of betamethasone or matching placebo 24 hours apart. The primary outcome was a neonatal composite of treatment in the first 72 hours (the use of continuous positive airway pressure or high-flow nasal cannula for at least 2 hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 4 hours, extracorporeal membrane oxygenation, or mechanical ventilation) or stillbirth or neonatal death within 72 hours after delivery.
RESULTS:
The primary outcome occurred in 165 of 1427 infants (11.6%) in the betamethasone group and 202 of 1400 (14.4%) in the placebo group (relative risk in the betamethasone group, 0.80; 95% confidence interval [CI], 0.66 to 0.97; P=0.02). Severe respiratory complications, transient tachypnea of the newborn, surfactant use, and bronchopulmonary dysplasia also occurred significantly less frequently in the betamethasone group. There were no significant between-group differences in the incidence of chorioamnionitis or neonatal sepsis. Neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001).
CONCLUSIONS:
Administration of betamethasone to women at risk for late preterm delivery significantly reduced the rate of neonatal respiratory complications. (Funded by the National Heart, Lung, and Blood Institute and the Eunice Kennedy Shriver National Institute of Child Health and Human Development; ClinicalTrials.gov number, NCT01222247.).

17. Pending PURL Review Date

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer if needed]

1. Number of patients starting each arm of the study?

2831 total: 1429 in intervention group, 1402 in placebo group

2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Women with a singleton pregnancy at 34 weeks 0 days gestational age (GA) to 36w 5d GA at high probability of delivery by 36w 3d GA (high probability defined as preterm labor either with SROM, or with intact membranes and at least 3cms cervical dilatation or 75% cervical effacement; or planned induction or cesarean section between 24 hours and 7 days after randomization). Women were excluded if they had received steroids previously in the pregnancy, or if they were expected to deliver in less than 12 hours.
3. Intervention(s) being investigated?	Antenatal steroids administered in the late preterm period for anticipated late preterm delivery to reduce the risk of respiratory and other complications
4. Comparison treatment(s), placebo, or nothing?	Placebo injections
5. Length of follow up? Note specified end points e.g. death, cure, etc.	Up to hospital discharge, neonatal death, or at 28 days after birth for infants receiving oxygen at the time of discharge
6. What outcome measures are used? List all that assess effectiveness.	Primary: A composite end point up to 72 hours of life consisting of the use of CPAP or high flow nasal cannula for at least 2 consecutive hours, supplemental O2 of at least 30% for at least 4 continuous hours, ECMO, stillbirth, or neonatal death. Secondary: severe respiratory complications (a composite of the use of CPAP or high-flow nasal cannua for at least 12 continuous hours, supplemental O2 of at least 30% for at least 24 hours, ECMO or mechanical ventilation, stillbirth, or neonatal death, all up to 72 hours of life), respiratory distress syndrome, transient tachypnea of the newborn (TTN), apnea, bronchopulmonary dysplasia (BPD), surfactant administration, need for resuscitation at birth, hypoglycemia, feeding difficulty, hypothermia, necrotizing enterocolitis, intraventricular hemorrhage, neonatal sepsis, pneumonia, death before discharge.
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	Absolute risk reduction [ARR] of the primary outcome 2.8%, relative risk [RR] 0.80, 95% CI, 0.66–0.97, number needed to treat [NNT]=35. ARR of severe respiratory complications 4%, RR 0.67, 95% CI, 0.53–0.84, NNT=25. ARR of TTN 3.2%, RR 0.68, 95% CI 0.53–0.87. ARR of BPD 0.5%, RR 0.22, 95% CI 0.02–0.92. ARR of resuscitation at birth 4.2%, RR 0.78, 95% CI 0.66–0.92. ARR of surfactant use 1.3%, RR 0.59, 95% CI 0.37–0.96.
8. What are the adverse effects of intervention compared with no intervention?	Higher incidence of neonatal hypoglycemia (Absolute risk increase 9%, RR 1.60, 95% CI 1.37–1.87.
9. Study addresses an appropriate and clearly focused question - ***select one***	Well covered Comments:
10. Random allocation to comparison groups	Well covered Comments:

11. Concealed allocation to comparison groups	Well covered Comments:
12. Subjects and investigators kept "blind" to comparison group allocation	Well covered Comments:
12. Comparison groups are similar at the start of the trial	Adequately addressed Comments: Maternal age and proportion of women of Hispanic origin different at start of trial; this was addressed in post-hoc analyses
14. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Well covered Comments: See answer to **12** above
15. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered Comments: "Tained and certified" research staff members did chart reviews of participants
16. Are patient oriented outcomes included? If yes, what are they?	Yes. Virtually all of the outcomes are patient-oriented
17. What percent dropped out, and were lost to follow up? Could this bias the results? How?	39.8% in the study group and 41.1% in the placebo group did not receive the two doses of either betamethasone of placebo. 2 women in each group were lost to follow-up. This should not bias the results.
18. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes
19. If a multi-site study, are results comparable for all sites?	Yes

20. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	Nope
21. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Pregnant women with threatened late preterm delivery
22. In what care settings might the findings apply, or not apply?	Clinics providing prenatal care and obstetrical units
23. To which clinicians or policy makers might the findings be relevant?	Obstetrical care providers

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions	For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year. EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.} For DynaMed, use the following style: Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}
1. DynaMed excerpts	Antenatal betamethasone improves respiratory outcomes in late preterm infants (level 1 [likely reliable] evidence). [Based exclusively on a review of the article under question here]
2. DynaMed citation/access date	Title. Review of management of preterm labor. Author. Beverly Siegal Peiser, MD, MPH In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated:2016 Apr 21 10:57:00 AM . Accessed 21 June 2016
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Antenatal betamethasone improves respiratory outcomes in late preterm infants (level 1 [likely reliable] evidence). [Based exclusively on a review of the article under question here]

4. UpToDate excerpts

UpToDate summarizes the article under review here, and adds "No data are available about the long-term neurodevelopmental outcomes of children exposed to corticosteroids between $34^{0/7ths}$ and $36^{5/7ths}$ weeks of gestation. This is a significant concern because active brain growth through cell division is occurring at this time and might be inhibited by administration of corticosteroids, which might afect neurodevelopment adversely."

"Based on the data described above, the authors take the following approach, which limits late preterm in utero steroid exposure to pregnancies certain to deliver preterm and with neonates at most risk for experiencing serious respiratory problems from transient tachypnea of the newborn.

●For women scheduled for cesarean delivery at $34^{0/7ths}$ to $36^{6/7ths}$ weeks, we believe offering a first course of antenatal corticosteroids to reduce neonatal respiratory morbidity is reasonable. While there may be short-term advantages to receiving steroids prior to cesarean at this gestational age, the risk-to-benefit ratio is unknown. Families should be informed and participate in the decision-making. We would not administer a second course of steroids at this gestational age to women who received steroids before 34 weeks as the benefits and risks have not been studied in this population. We also would not administer steroids to women undergoing scheduled cesarean delivery at ≥37 weeks: The overall risk of neonatal respiratory illness at this gestational age is low and rarely serious.

●For women in whom vaginal delivery at $\geq 34^{0/7ths}$ weeks is expected, we would not administer a first course of steroids as transient tachypnea of the newborn is less common after labor and vaginal birth.

●For women in whom delivery at $34^{0/7th}$s to $36^{6/7ths}$ is uncertain (eg, threatened preterm labor), we would not administer a course of steroids because of the potential for long-term harm with no benefit if the patient does not deliver preterm."

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Antenatal corticosteroid therapy for reduction of neonatal morbidity and mortality from preterm delivery. Author. Lee M, Guinn D In: Basow DS, ed. UpToDate [database online] Waltham, Mass: UpToDate; 2016. Available at: http://www.uptodate.com. Last updated: 8 April 2016 . Accessed 21 June 2016

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

Give antenatal steroids scheduled for late preterm delivery if not given previously.

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
Yes, there is important evidence or recommendations that are missing
No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
Yes, there is important evidence or recommendations that are missing
No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts (USPSTF; other guidelines; etc.)

Society for Maternal-Fetal Medicine recommendations:
1. In women with a singleton pregnancy between 34 weeks 0 days and 36 weeks 6 days of gestation who are at high risk for preterm birth within the next 7 days (but before 37 weeks of gestation), we recommend treatment with betamethasone (1 doses of 12 mg intramuscularly 24 hours apart).
2. In women with preterm labor symptoms in the late preterm period, we recommend waiting for evidence of preterm labor, such as a cervical dilatation of at least 3 cm or effacement of at least 75%, before treatment with betamethasone.
3. In women with late preterm pregnancies receiving betamethasone, we recommend against the use of tocolysis in an attempt to delay delivery to complete the steroid course because it is unclear whether the benefits of betamethasone administration are outweighed by the risks of attempts to delay delivery.
4. In women with late preterm pregnancies with a potential medical indication for delivery, we recommend betamethasone not be given unless there is a definitive plan for late preterm delivery.
5. We recommend that institutions utilize standard guidelines for the assessment and management of neonatal hypoglycemia in late preterm newborns.
6. We recommend against implementation of the Antenatal Late Preterm Steroids protocol for conditions not studied in the randomized controlled trial unless performed as part of research or quality improvement.

ACOG Practice Advisory (endorsed by AAP)
With the release of this new data and until further guidance is released, 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.

Monitoring of neonatal blood glucose is recommended for late preterm infants since late preterm birth is a risk factor for hypoglycemia; these same guidelines should be followed for infants exposed to antenatal corticosteroids administered during the late preterm period.

Late preterm antenatal corticosteroid administration should not be used in women diagnosed with chorioamnionitis (intrauterine infection).

Tocolysis should not be used in order to delay delivery to allow for administration of late preterm antenatal corticosteroids, nor should an indicated late preterm delivery (such as for preeclampsia with severe features) be postponed for steroid administration.

Administration of late preterm antenatal corticosteroids should not be given if the pregnancy was already exposed to antenatal corticosteroids.

Because the ALPS trial excluded pregnant women with diabetes, multifetal gestations, previous exposure to steroids during pregnancy, or pregnancies with major non-lethal fetal malformations, ACOG is reviewing these topics and will issue any updated clinical guidance as appropriate.

11. Citations for other excerpts	For MFM statement (article in press): http://dx.doi.org/10.1016/j.ajog.2016.03.013 For ACOG Practice advisory: http://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Antenatal-Corticosteroid-Administration-in-the-Late-Preterm-Period Updated April 4, 2016; accessed 21 June, 2016
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	With some caveats, steroids may be administered to women at risk of late preterm birth

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) 1
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?	Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly) 1
4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.	
5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?	Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice) 1

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	Before this study, no recommendation to give antenatal steroids to women past 34 weeks GA. The practice change is administering steroids to women at risk for late preterm (34w0d to 36w6d) delivery in order to reduce the risk of neonatal respiratory complications
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?	Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting) 1
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.	
9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?	Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied) 1
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	
11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented?	Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented) 1

12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.	
13. In your opinion, is this a Pending PURL? Criteria for a Pending PURL: • Valid: Strong internal scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) 1
14. Comments on your response in 4.13	Practice recommendations from the major specialty societies have already changed on the basis of this study.