Antenatal steroids after 34 weeks – wise precaution or unnecessary risk?

Cape Town November 2015

P J Steer
Professor of Obstetrics
Academic Department of Obstetrics and Gynaecology
Chelsea and Westminster Hospital
Antenatal betamethasone for the prevention of RDS

- Significant reduction in the incidence of RDS in infants <32 weeks gestation at birth when mothers were treated with betamethasone for 2-7 days before delivery

Liggins GC and Howie RN, Pediatrics 50;515-525, 1972
ANTENATAL STEROIDS FOR THE PREVENTION OF RESPIRATORY DISTRESS SYNDROME

Crowley, P. Cochrane meta-analysis of 15 trials, 1996
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>08.35 - 09.00</td>
<td>Opening Ceremony</td>
</tr>
</tbody>
</table>
| 09.00 - 09.45    | Plenary Lecture 1
                  | The Steroid Story: Iconic Advance or Ticking Bomb?                 |
                  | John Newnham, Australia PL1                                          |

Newnham JP, Moss TJ, Nitsos I, Sloboda DM.
Antenatal corticosteroids: the good, the bad and the unknown.
RISKS OF ANTENATAL STEROIDS

• In animal studies, steroids delay myelination in the fetal brain and reduces the growth of all fetal brain areas particularly the hippocampus

• In humans, decreased birthweight

• an increase in behavioural disorders at 3 years of age

RISKS OF ANTENATAL STEROIDS (2)

• long-term effects on the setting of the hypothalamo-pituitary axis and glucose homeostasis\(^4\)

• higher systolic and diastolic blood pressures in adolescence, and possible clinical hypertension in survivors well beyond birth\(^5\)


If one course of steroids is good.....

Then multiple courses must be even better
Practice in the UK 1997

A survey of practice was carried out in the UK in 1997

- 98% of responding units prescribe multiple courses of antenatal steroids

MULTIPLE COURSES OF ANTENATAL STEROIDS - BENEFIT OR HARM?

- Multiple courses were not shown to confer additional benefits. 

- Multiple courses of antenatal betamethasone are associated with increased risks of perinatal infectious morbidity and neonatal death. 

- In humans, decreased neonatal head circumference 
  *Walfisch A, Hallak M, Mazor M. Obstet Gynecol 2001;98:491-7*
11. When should an antenatal course of corticosteroids be repeated?

Weekly repeat courses of antenatal corticosteroids reduce the occurrence and severity of neonatal respiratory disease, but the short-term benefits are associated with a reduction in weight and head circumference. Weekly repeat courses are not recommended.

A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26th weeks of gestation. Senior opinion should be sought if a rescue course is to be considered.
Effect of Antenatal Corticosteroids on Fetal Growth and Gestational Age at Birth

Kellie E. Murphy, MD, Andrew R. Willen, MD, Mary E. Hanna, MDS, Arne Oldsjo, MD, Edmond N. Kelly, MB, Stephen G. Mullinex, MD, Sairaj Suigal, MD, Elizabeth Aztahos, MD, Susan Ross, MD, Marie-France Delsi, MD, Kofi Ameakwah, MD, Patricia Guselle, MS, Aniram Gajra, BS, Shuo K. Lee, MB, BS, and E. Anthony Arsonso, MD, for the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study Collaborative Group*

OBJECTIVE: To estimate the effect of multiple courses of antenatal corticosteroids on neonatal size, controlling for gestational age at birth and other confounders, and to determine whether there was a dose–response relationship between number of courses of antenatal corticosteroids and neonatal size.

METHODS: This is a secondary analysis of the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study, a double-blind randomized controlled trial of single compared with multiple courses of antenatal corticosteroids in women at risk for preterm birth and in which fetuses administered multiple courses of antenatal corticosteroids weighed less, were shorter, and had smaller head circumferences at birth. All women (n=1,858) and children (n=2,384) enrolled in the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study were included in the current analysis. Multiple linear regression analyses were undertaken.

RESULTS: Compared with placebo, neonates in the antenatal corticosteroids group were born earlier estimated difference and confidence interval [CI] −0.426 weeks, CI −0.750 to −0.026, P=0.031. Controlling for gestational age at birth and confounding factors, multiple courses of antenatal corticosteroids were associated with a decrease in birth weight (−3.350 g, CI −6.679 to −0.022, P=0.045), length (−0.639 cm, CI −0.967 to −0.311, P=0.019), and head circumference (−0.129 cm, CI −0.255 to −0.003, P=0.052). For each additional course of antenatal corticosteroids, there was a trend toward an incremental decrease in birth weight, length, and head circumference.

CONCLUSION: Fetuses exposed to multiple courses of antenatal corticosteroids were smaller at birth. The reduction in size was partially attributed to being born at an earlier gestational age but also was attributed to decreased fetal growth. Finally, a dose–response relationship exists between the number of corticosteroid courses and a decrease in fetal growth. The long-term effect of these findings is unknown.

*For a list of other members of the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study collaboration group, see the Appendix online at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1554-8200/issue.

From the Department of Obstetrics and Gynecology, Mount Sinai Hospital, the Program in Child Health Evaluation Sciences, SickKids Research Institute and Division of Neonatology, the Departments of Obstetrics and Gynaecology and Newborn and Developmental Pediatrics and the Centre for Mother, Infant, and Child Research, SickKids Health Sciences Centre, the Departments of Physiology, Obstetrics and Gynaecology, and Medicine, and the Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; the Department of Paediatrics and the Centre for Health Economics and Policy Analysis, and the Department of Clinical Epidemiology and Biostatistics, McMaster University Medical Centre, Hamilton, Ontario, Canada; the Department of Obstetrics and Gynaecology, University of Calgary, Calgary, Alberta, Canada; the Women’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada; the Cleveland Clinic Foundation, Cleveland, Ohio, USA; the University of New Mexico School of Medicine, Albuquerque, New Mexico, USA; and the Division of Neonatology, Hospital for Sick Children, Toronto, Ontario, Canada. Supported by Canadian Institutes of Health Research grant number MOP-81422.

Corresponding author: Kellie E. Murphy, MD, MS, FRCS(C), FRCOG, Mount Sinai Hospital, Maternal Fetal Medicine, Department of Obstetrics and Gynecology, 3rd Floor, Room 8437, Toronto, Canada (kellie.murphy@sickkids.ca).

Financial Disclosure: The authors did not report any potential conflict of interest.

© 2012 by The American College of Obstetricians and Gynecologists. Published by Lippincott Williams & Wilkins.
ISSN: 0003-0932/12

CONCLUSION: Fetuses exposed to multiple courses of antenatal corticosteroids were smaller at birth. The reduction in size was partially attributed to being born at an earlier gestational age but also was attributed to decreased fetal growth. Finally, a dose–response relationship exists between the number of corticosteroid courses and a decrease in fetal growth. The long-term effect of these findings is unknown.

CORONAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT00187302.
DOI: 10.1097/AOG.0b013e31825782e6

LEVEL OF EVIDENCE: II

The Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study was an international, multicenter, double-blind, randomized controlled trial of single compared with multiple courses of
Is a single course safe?

- 30-31 years follow up of Auckland randomised controlled trial of antenatal betamethasone – 1218 babies born
- 75 g oral glucose tolerance test
- Participants exposed to betamethasone had significantly higher plasma insulin concentrations at 30 min (60.5 vs 52.0 mIU/L) and lower glucose concentrations at 120 min (4.8 vs 5.1 mmol/L)
- “Our findings of changes in the glucose-insulin axis provide experimental evidence to lend support to the glucocorticoid hypothesis for the fetal origins of adult disease”

Dalziel SR et al:
BMJ. 2005 Sep 24;331(7518) : Lancet. 2005 May 28-Jun 3;365(9474):1856-62
The long-term effects of exogenous glucocorticoid exposure in late pregnancy for these children are unknown.

- data in a nonhuman primate model suggest dose-associated programming of cardiometabolic parameters

- the lowest dose of glucocorticoid possible should be used to minimize long-term adverse effects
Kelly et al, Pediatrics 2012 128:1283-90

- Glucocorticoid exposure is associated with a localized increase in aortic arch stiffness, similar in magnitude to term born individuals a decade older. The change in stiffness does not relate to changes in glucose metabolism that were also evident in this cohort.
This is the first demonstration that synthetic glucocorticoid doses in the clinical range have multigenerational effects on hypothalamo-pituitary-adrenal activity in precocial species, indicating the need for the study of long-term effects of fetal synthetic glucocorticoid exposure.
Outcome at 5 years of age

- 1719 subjects; 871 given steroids fortnightly
- No benefits of multiple courses found
- Odds ratio of neurosensory disability in babies born at term following multiple courses = 3.7 (1.57-8.75), P=0.005

Antenatal corticosteroids have no known benefits for the mother.

5. **At what gestation should antenatal steroids be used?**
Clinicians should offer a single course of antenatal corticosteroids to women between 24^{0} and 34^{6} weeks of gestation who are at risk of preterm birth.

9. **Who should receive antenatal corticosteroids?**
Antenatal corticosteroids should be given to all women at risk of iatrogenic or spontaneous preterm birth up to 34^{6} weeks of gestation.

Antenatal corticosteroids should be given to all women for whom an elective caesarean section is planned prior to 38^{6} weeks of gestation.
Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial

Peter Stutchfield, Rhiannon Whitaker, Ian Russell, on behalf of the Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team
Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial.

- Stutchfield P1, Whitaker R, Russell I; Antenatal Steroids for Term Elective Caesarean Section (ASTECS) Research Team.

Elective delivery at term

Incidence Of ‘RDS’ %

Weeks gestation

A single course of steroids reduces neonatal mortality in babies born before 34 weeks and this perhaps justifies the small risk of long-term side-effects. However, no such substantial benefit has been shown after this gestation. Delaying delivery until 39 weeks, unless necessary, would seem a more prudent option than giving steroids whose long-term safety, even as a single course, remains questionable.
David Hutchon, rapid response 9th October 2005

- Treatment group 26/467 (5.6%) admitted to SCBU for any reason
- Controls 32/475 (6.7%)
- Relative risk for neonatal admission following steroids of 0.82 (95% confidence interval 0.5 – 1.37)
The study was not powered or designed to show a difference in the total admission rate, merely the difference in the numbers admitted with respiratory distress.

If a larger study was designed and adequately powered to show an overall difference in all admissions, we are confident that a reduction would be seen as a direct result of fewer admitted with respiratory distress.
Stutchfield trial follow-up

• Lower rate of respiratory morbidity in steroid treated vs controls at age 8-15 years – 2% vs 9%
• No difference in hospital admissions or asthma
• Low academic achievement significantly more common after steroids – 17.7% vs 8.5% (p=0.01)

Aiken et al 2014

• “a lack of effect of glucocorticoids on cognitive function following birth at term cannot safely be inferred by the apparent absence of an adverse effect in the context of preterm birth”

• “exposing the fetus or neonate to potent synthetic may cause an early switch to differentiation and maturation in the developing brain”

• “It is plausible that this could result in adverse effects on long-term neurodevelopmental outcome”

Aiken et al 2014

• “The question facing obstetricians and neonatologists is whether this degree of reduction in short-term respiratory morbidity justifies the risk that glucocorticoids may have an adverse effect on cognitive function of the child in later life. Given the present evidence, we do not believe the risk is warranted”
Overall benefit

Babies born preterm
- Benefit > harm

Babies born at term
- No obvious benefit
- BUT
- Harm persists?
Risk of adverse effects on babies born at term

- Significantly higher rate of low 5 minute Apgar scores\(^1\)
- Trend to increase in SGA\(^1\)
- Significantly increased cortisol reactivity to acute psychosocial stress in 6- to 11-yr-olds\(^2\)

A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to the preterm birth in low income and middle income countries: the ACT cluster randomised trial

Lancet. 2015 Feb 14;385(9968):629-39

- October 2011 – March 2014
- Argentina, Guatemala, India, Kenya, Pakistan, and Zambia
- 51 Intervention clusters with 47,394 livebirths
- 50 Control clusters with 50,743 livebirths
- Antenatal steroids: 45% vs 10%

Despite increased use of antenatal corticosteroids in low birthweight infants in the intervention groups, neonatal mortality did not decrease in this group, and increase in the population overall. For every thousand women exposed to this strategy, an excess of 3.5 neonatal deaths occurred, and the risk of maternal infection seems to have been increased
“An unexpected and unfortunate finding was that the intervention resulted in an 11–12% relative increase in neonatal and perinatal mortality in the whole population.”

“This harmful effect was concentrated in infants at and above the 25th birthweight percentile, in whom the relative increase in mortality was 30%. Gestational age-based analysis showed a similar effect for term infants.”
How common is it for mothers given corticosteroids preterm to deliver at term?

- Texas Women’s Hospital\(^1\)
  - of 692 cases, 36% delivered \(\geq 34\) weeks

- National Maternity Hospital, Dublin\(^2\)
  - of 277 cases, 80% delivered \(\geq 34\) weeks

- Nova Scotia, Canada\(^3\)
  - Of 1,410 cases, 50% delivered \(>34\) weeks

“for every suspected preterm delivery giving rise to an infant born before gestational week 34 there will be another one or two infants born at a later gestational age”

for whom

“the benefits of the ACS administration, which they will most likely receive, are less obvious”

Antenatal corticosteroids: A time for more careful scrutiny of the indications?

Vidaeff A, Belfort M and Steer P

BJOG – In Press
Conclusions

• Antenatal corticosteroid administration was a big step forward in improving the outcome in preterm birth

• But you can have too much of a good thing – multiple courses should be avoided

• Don’t give it after 35 weeks

• We need to improve our prediction of babies who will actually deliver preterm so as to avoid administration of steroids to babies who cannot benefit and may be harmed