Imperial College
London

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

Cape Town November 2015

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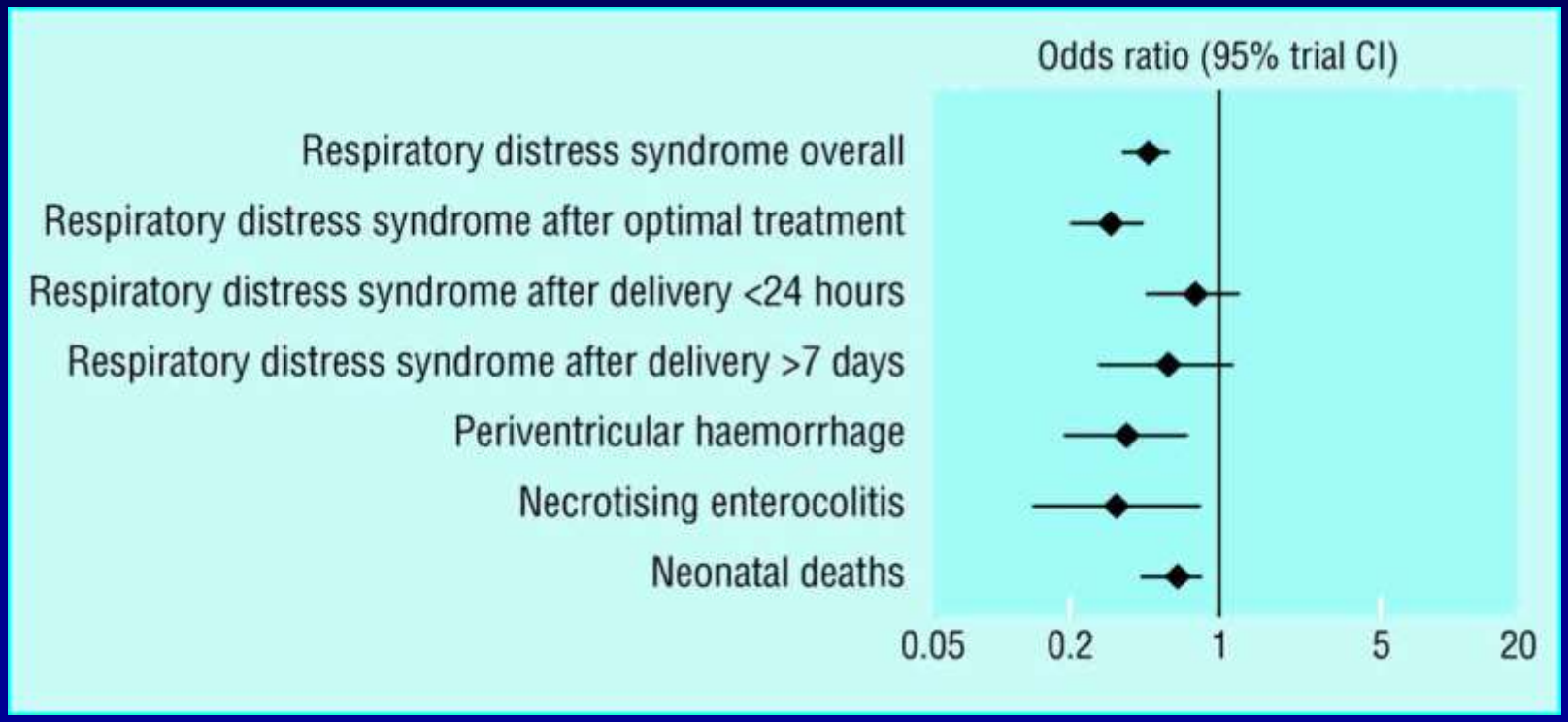
Antenatal betamethasone for the prevention of RDS

- 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

	Clyde Auditorium
08.35 - 09.00	**Opening Ceremony**
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.
Curr.Opin.Obstet.Gynecol. 2002;**14**:607-12.

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[1]
- In humans, decreased birthweight[2]
- an increase in behavioural disorders at 3 years of age[3]

1. Whitelaw A,.Thoresen M. Antenatal steroids and the developing brain.
Arch Dis Child Fetal Neonatal Ed 2000;**83**:F154-F157.
2. Bloom SL, Sheffield JS, McIntire DD, Leveno KJ. Antenatal dexamethasone and decreased birth weight.
Obstet.Gynecol. 2001;**97**:485-90.
3. Newnham JP, Moss TJ, Nitsos I, Sloboda DM. Antenatal corticosteroids: the good, the bad and the unknown.
Curr.Opin.Obstet.Gynecol. 2002;**14**:607-12.

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]

4. Welberg LA, Seckl JR, Holmes MC. Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. *Neuroscience* 2001;**104**:71-9.

5. Doyle LW, Ford GW, Davis NM, Callanan C. Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children. *Clin.Sci.(Lond)* 2000;**98**:137-42**.**

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

Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain GVP. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. British Journal of Obstetrics and Gynaecology 1999; 106; 977-979.

MULTIPLE COURSES OF ANTENATAL STEROIDS - BENEFIT OR HARM?

- Multiple courses were not shown to confer additional benefits.
  L. M. Smith et al, J Matern Fetal Med 9 (2):131-135, 2000.

- Multiple courses of antenatal betamethasone are associated with increased risks of perinatal infectious morbidity and neonatal death.
  S. T. Vermillion, *et al*. *Am J Obstet Gynecol* 183 (4):810-814, 2000.

- In humans, decreased neonatal head circumference
  Walfisch A, Hallak M, Mazor M. Obstet Gynecol 2001;98:491-7

Royal College of Obstetricians & Gynaecologists

Antenatal Corticosteroids to Reduce Neonatal Morbidity and Mortality

Green–top Guideline No. 7

October 2010

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**

A single rescue course may be considered with caution in pregnancies where the initial course was given at less than 26^{+0} 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. Willan, PhD, Mary E. Hannah, MDCM, Arne Ohlsson, MD, Edmond N. Kelly, MB, Stephen G. Matthews, PhD, Saroj Saigal, MD, Elizabeth Asztalos, MD, Susan Ross, PhD, Marie-France Delisle, MD, Kofi Amankwah, MD, Patricia Guselle, MSc, Amiram Gafni, DSc, Shoo K. Lee, MB, BS, and B. Anthony Armson, 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=2,304) 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]: −0.428 weeks, CI −0.10264 to −0.75336; *P*=.01). Controlling for gestational age at birth and confounding factors, multiple courses of antenatal corticosteroids were associated with a decrease in birth weight (−33.50 g, CI −66.27120 to −0.72880; *P*=.045), length (−0.339 cm, CI −0.6212 to −0.05676]; *P*=.019), and head circumference (−0.296 cm, −0.45672 to −0.13528; *P*<.001). 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.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00187382.

(Obstet Gynecol 2012;119:917–23)

DOI: 10.1097/AOG.0b013e31825189dc

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

**For a list of other members of the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study collaborative group, see the Appendix online at http://links.lww.com/AOG/A296.*

From the Departments of Obstetrics and Gynaecology and Paediatrics, Mount Sinai Hospital, the Program in Child Health Evaluative Sciences, SickKids Research Institute and Division of Biostatistics, the Departments of Obstetrics and Gynaecology and Newborn & Developmental Paediatrics and the Centre for Mother, Infant and Child Research, Sunnybrook Health Sciences Centre, the Departments of Physiology, Obstetrics and Gynecology, 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 Departments of Obstetrics and Gynaecology, University of Calgary, Calgary, Alberta, Canada, BC Women's Hospital, University of British Columbia, Vancouver, British Columbia, Canada, and IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada; the Department of Gynecology-Obstetrics, Women's and Children's Hospital, State University of New York at Buffalo, Buffalo, New York; and the Division of Neonatology, Hospital for Sick Children, Toronto, Ontario, Canada.

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Financial Disclosure

The authors did not report any potential conflicts of interest.

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Green Journal 2012

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.

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

J Clin Endocrinol Metab October 2012 **97:**3457-9
Reynolds RM and Seckl JR

- 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 turn born individuals a decade older. The change in stiffness does not relate to changes in glucose metabolism that were also evident in this cohort

Long, BN et al, Am J Obstet Gynecol 2013;208:217.e1-8

- 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

Asztalos et al, JAMA Pediatr. 2013;167(12):1102-1110

RCOG greentop guidelines number 7 2010

Antenatal corticosteroids have no known benefits for the mother. **A**

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. **A**

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. **A**

Antenatal corticosteroids should be given to all women for whom an elective caesarean section is planned prior to 38^{+6} weeks of gestation. **A**

Cite this article as: BMJ, doi:10.1136/bmj.38547.416493.06 (published 22 August 2005)

Papers

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

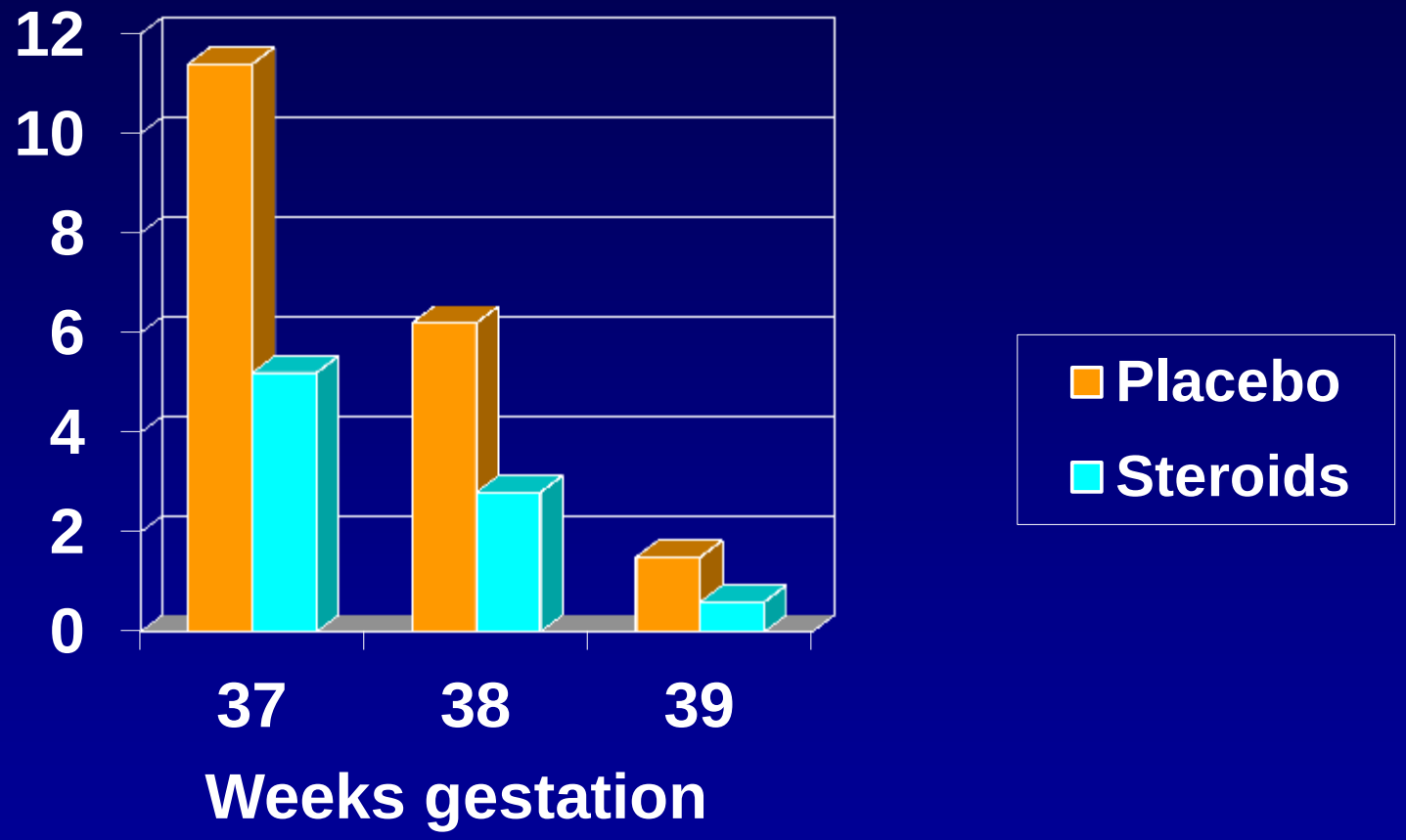
Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial.

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

- BMJ. 2005 Sep 24;331(7518):662. Epub 2005 Aug 22.

Elective delivery at term

Incidence Of 'RDS' %



Stutchfield P et al: BMJ. 2005 Sep 24;331(7518):662.

Giving steroids before elective caesarean section.

Steer PJ.

BMJ. 2005 Sep 24;331(7518):645-6.

- 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)

Stutchfield reply BMJ 14 December 2005

- 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)

Stutchfield PR et al Arch Dis Child Fetal Neonatal Ed. May 2013; 98(3): F195–F200

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 C et al, JAMA Pediatrics June 2014;168:507-509

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]

1. Eriksson L *et al* Acta Obstet Gynecol Scand 2012;91:1415–1421.
2. Alexander N *et al* J Clin Endocrinol Metab 2012;97: 3538–3544

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 >=34 weeks
- National Maternity Hospital, Dublin[2]
  - of 277 cases, 80% delivered >=34 weeks
- Nova Scotia, Canada[3]
  - Of 1,410 cases, 50% delivered >34 weeks

1. Davidson C *et al* J Reprod Med 2010; 55(1-2):14-18
2. Mahony R, *et al* BJOG 2010; 117(8):963-967
3. Razaz N *et al* Obstet Gynecol 2015; 125(2):288-296

“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”

Eriksson L et al Acta Obstet Gynecol Scand 2012;91:1415–1421

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