Title of Program: Antenatal strategies: steroids, magnesium, and best obstetric practices

Speakers/Moderators: Roger F. Soll, Ira Bernstein, Danielle Ehret

Planning Committee: Jeffery D. Horbar, Madge E. Buus-Frank, Roger F. Soll

Date: June 13, 2018

Learning Objectives:
The goal of this session is for participants to be able to assess the evidence for various antenatal interventions including antenatal steroids, antenatal magnesium sulfate and other obstetric practices. Participants will also be able to assess appropriateness of current recommendations and practices for various populations and identify gaps in current antenatal obstetric practice compared to evidence based recommendations.

DISCLOSURE:

Is there anything to disclose? *No financial interests to disclose*

COMMERCIAL SUPPORT ORGANIZATIONS *(if applicable):* *No Commercial Support*

In support of improving patient care, this activity has been planned and implemented by The Robert Larner College of Medicine at The University of Vermont and Cochrane Neonatal. The University of Vermont is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The University of Vermont designates this live activity for a maximum of *1 AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This program has been reviewed and is acceptable for up to 1 Nursing Contact Hours.

Cochrane Neonatal

Antenatal strategies: steroids, magnesium, and best obstetric practices

Roger F. Soll, MD
H. Wallace Professor of Neonatology
University of Vermont College of Medicine

Coordinating Editor, Cochrane Neonatal
President, Vermont Oxford Network

Cochrane Web Seminar June 28th 2018

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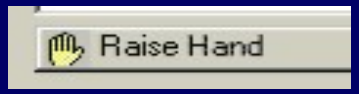

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Preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions

Cochrane Neonatal

Prepares and disseminates evidence-based reviews of the effects of therapies in the field of neonatal medicine

Cochrane Neonatal

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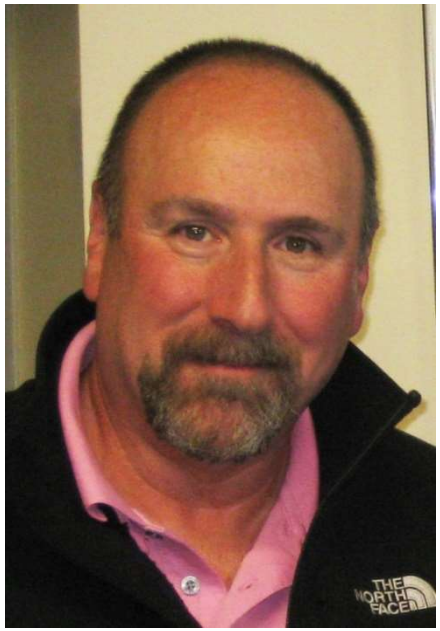

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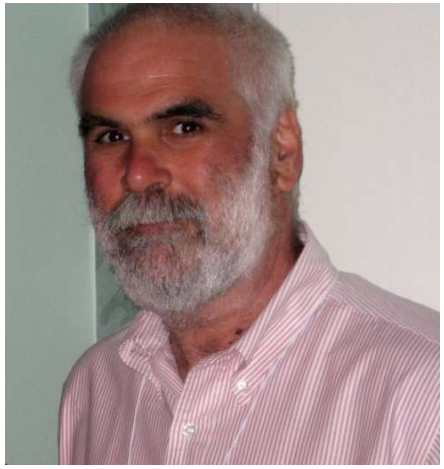

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Disclosure

Roger F. Soll is the Coordinating Editor of Cochrane Neonatal and President of Vermont Oxford Network

Evidence Based Medicine

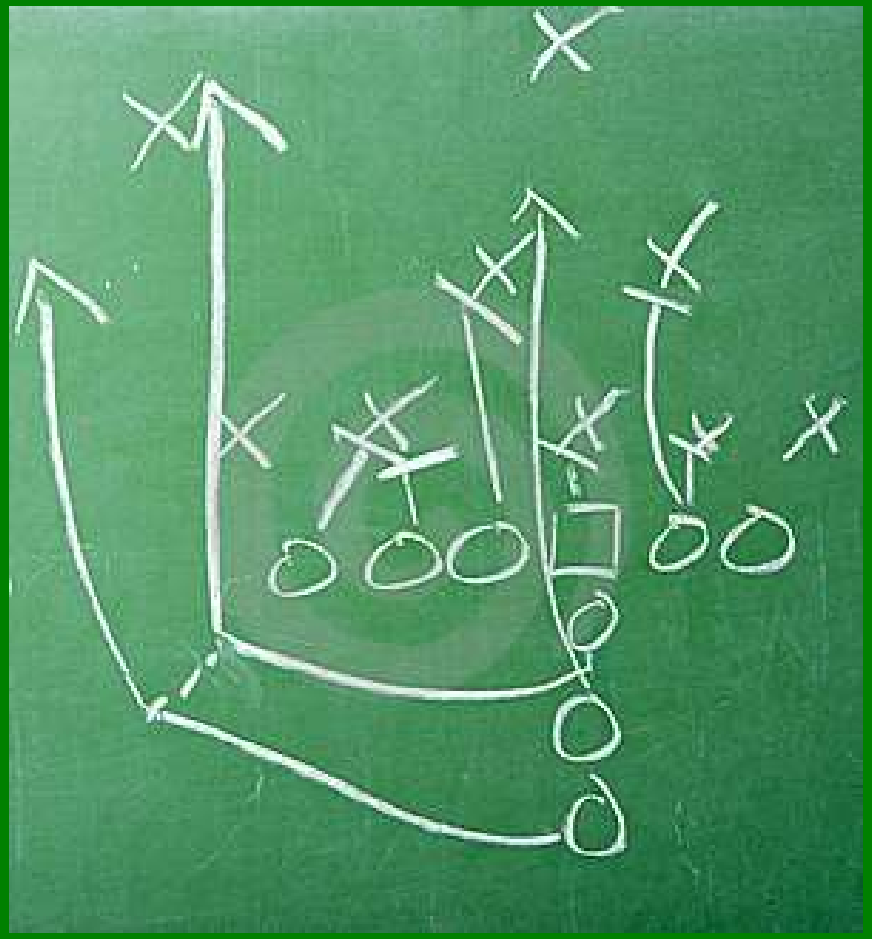
Vermont Oxford Network 2016

Infants Gestational Age 22 to 29 Weeks

	Lowest Quartile	Highest Quartile
Antenatal Steroids	77%	93%
Antenatal MgSO4	36%	77%
Cesarian Section	60%	77%

Over 42,000 Infants at NICUs in the Vermont Oxford Network

Evidence Based Medicine



If we are all reading the same information…

Why aren’t we operating from the same playbook?

The Scope of the Problem

Preterm birth, defined as birth occurring between 20 and 36 completed weeks of gestation is a major contributor to perinatal mortality and morbidity.

The rate of preterm birth is increasing across low- and middle-income countries, affecting 8.6% of births in high-income countries and between 7.4% to 13.3% in low- and middle-income countries (WHO 2012).

Preterm birth is a leading cause of perinatal morbidity including respiratory distress syndrome (RDS), chronic lung disease, intraventricular hemorrhage (IVH), sepsis, cerebral palsy and other forms of neurodevelopmental impairment (Gladstone 2011), blindness and deafness.

The costs to the parents, community and society as a whole, both economic and emotional, are substantial (Petrou 2011).

The Scope of the Problem

Approximately 65% to 70% are spontaneous preterm births either following spontaneous preterm labor (40% to 45%) or following preterm rupture of membranes (25% to 30%) (Goldenberg 2008).

While the cause of spontaneous preterm birth is often unclear, some risk factors have been identified including:

1. maternal age (adolescence and advanced age); 2. history of preterm birth; 3. race; 4. multiple pregnancy, 5. short inter-pregnancy interval; 6. infections; 7. medical conditions; 8. poor nutrition; 9. psychological factors and 10. genetic predisposition (Goldenberg 2008).

Despite improvements in the standards in obstetric and neonatal care over recent years, no progress has been made over the last two decades in reducing the incidence of preterm birth in high-income countries. In fact, rates of preterm birth are rising, in part due to increasing obstetric intervention (Goldenberg 2008; Norman 2009).

Antenatal Interventions to Prevent or Improve the Outcome of Preterm Delivery

- Tocolytic agents
- Neuroprotection
- Antenatal Steroids
- Caesarian Section
- Cord Clamping
- Antibiotics

Tocolytic Agents

Tocolytic drugs have been used to inhibit preterm labor, in order to allow time for co-intervention and potentially to defer preterm birth, thus improving neonatal outcomes with advancing gestation.

A range of tocolytic agents that have been used to inhibit preterm labor are the topics of Cochrane systematic reviews including:

Betamimetics (Neilson 2014)
Calcium channel blockers (Flenady 2014)
Magnesium sulfate (Crowther 2014)
Cyclo-oxygenase (COX) inhibitors (Reinebrant 2015)
Progesterone (Su 2014)

and their relative effects have been explored in a recent network meta-analysis (Haas 2012).

Cochrane Library

Cochrane Database of Systematic Reviews

Betamimetics for inhibiting preterm labour (Review)

Neilson JP, West HM, Dowswell T

Neilson JP, West HM, Dowswell T.
Betamimetics for inhibiting preterm labour.
Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD004352.
DOI: 10.1002/14651858.CD004352.pub3.

Betamimetics for inhibiting preterm labor

Mechanism of action:

β-Adrenoreceptor agonists, such as ritodrine and terbutaline, have been used since the 1970s in the treatment of threatened preterm birth.

β-Adrenoreceptor agonists activate adenyl cyclase to form cyclic adenosine monophosphate.

By reducing intracellular calcium through increasing calcium uptake by sarcoplasmic reticulum and phosphorylation of the myosin light-chain kinase, β-adrenoreceptor agonists decrease myosin light-chain kinase activity, resulting in myometrial relaxation.

Betamimetics for inhibiting preterm labor

Results:

Eleven randomized controlled trials, involving 1332 women, compared betamimetics with placebo.

Betamimetics decreased the number of women in preterm labor giving birth within 48 hours

- relative risk (RR) 0.63; 95% confidence interval (CI) 0.53 to 0.75

(however, there was no decrease in the number of births within seven days after carrying out a sensitivity analysis of studies with adequate allocation of concealment).

No benefit was demonstrated for betamimetics on

- perinatal death (RR 0.84; 95% CI 0.46 to 1.55, 7 trials, n = 1332), or
- neonatal death (RR 1.00; 95% CI 0.48 to 2.09, 5 trials, n = 1174).

No significant effect was demonstrated for respiratory distress syndrome (RR 0.87; 95% CI 0.71 to 1.08, 8 trials, n = 1239). A few trials reported the following outcomes, with no difference detected: cerebral palsy, infant death and necrotizing enterocolitis.

Betamimetics for inhibiting preterm labor

Betamimetics have a high frequency of unpleasant, sometimes severe maternal side effects including:

- tachycardia;
- hypotension;
- tremor;
- biochemical disturbances;
- life-threatening cardiovascular and respiratory events and deaths.

Other Tocolytic Agents

A range of other tocolytic agents that have been used to inhibit preterm labor are the topics of Cochrane systematic reviews including:

Calcium channel blockers (Flenady 2014): 38 included trials (3550 women).
Cyclo-oxygenase inhibitors (Reinebrant 2015): 20 studies including (1509 women).
Progesterone (Su 2014): 8 studies (563 women)
Magnesium sulfate (Crowther 2014): 37 included trials (3571 women)

Other Tocolytic Agents: Rationale

Calcium channel blockers (Flenady 2014): Calcium channel blockers (CCBs) or calcium antagonists are non-specific smooth muscle relaxants, predominantly used for the treatment of hypertension in adults and are increasingly used as a tocolytic agent for women in preterm labor.

Calcium channel blockers, such as nifedipine, prevent the influx of extracellular calcium ions into the myometrial cell.

Other Tocolytic Agents: Rationale

Cyclo-oxygenase (COX) inhibitors (Reinebrant 2015)

Prostaglandins induce contractions of the uterine muscle by enhancing myometrial gap-junction formation and increasing intracellular calcium concentration.

COX enzymes are essential in the production of prostaglandins. The inhibition of COX enzymes results in reduced production of prostaglandins, thereby reducing uterine contractions

Cyclo-oxygenase (COX) inhibitors are easily administered and appear to have few maternal side effects.

However, adverse effects have been reported in the fetus and newborn as a result of exposure to COX inhibitors.

Other Tocolytic Agents: Rationale

Progesterone (Su 2014)

Progesterone is known to have an inhibitory effect on uterine contractility and is thought to play a key role in the maintenance of pregnancy until term.

Eight studies were included in this review, involving 563 women, but only seven studies, involving 538 women, contributed data for analyses. There are some data suggesting that the use of progestational agents results in a reduction of preterm deliveries at less than 37 weeks of gestation and an increase in birthweight.

The use of a progestational agent may also reduce the frequency of uterine contractions, prolong pregnancy and attenuate the shortening of cervical length. However, the analysis was limited by the relatively small number of available studies. The power of the meta-analysis was also limited by the varying types, dosages and routes of administration of progesterone.

Other Tocolytic Agents: Rationale

Magnesium sulfate (Crowther 2014)

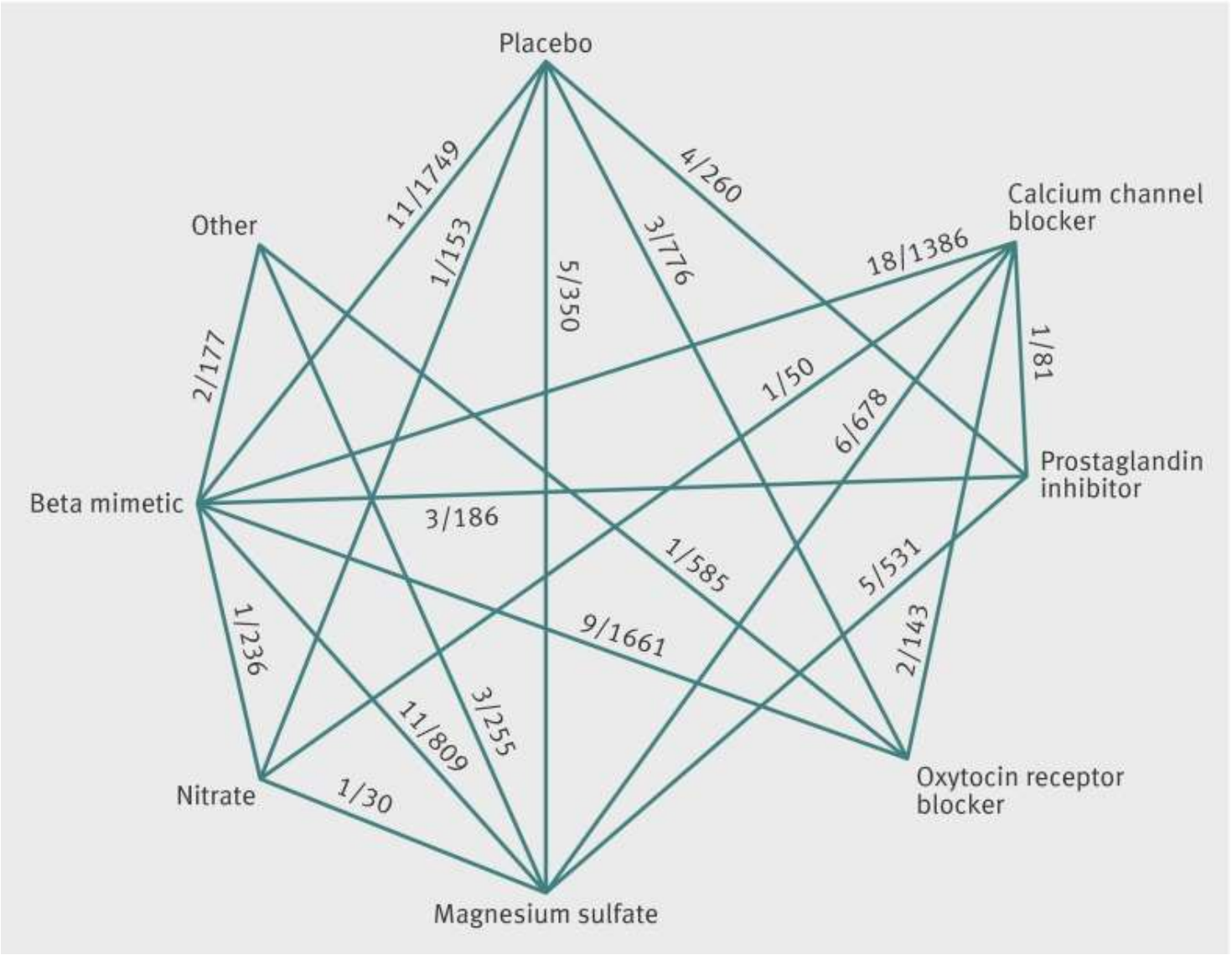
Magnesium reduces the frequency of depolarization of smooth muscle by modulating calcium uptake, binding, and distribution in smooth muscle cells. This results in inhibition of uterine contractions

Tocolytic therapy for preterm delivery: systematic review and network meta-analysis.

Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ.

BMJ 2012;345:e6226.

95 randomized controlled trials of tocolytic therapy



Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012;345:e6226.

Tocolytic therapy for preterm delivery: systematic review and network meta-analysis.

Compared with placebo, the probability of delivery being delayed by 48 hours was highest with:

- prostaglandin inhibitors (odds ratio 5.39, 95% CI 2.14 to 12.34)
- magnesium sulfate (odds ratio 2.76, 95% CI 1.58 to 4.94)
- calcium channel blockers (odds ratio 2.71, 95% CI 1.17 to 5.91)
- beta mimetics (odds ratio 2.41, 95% CI 1.27 to 4.55)
- oxytocin receptor blocker atosiban (odds ratio 2.02, 95% CI 1.10 to 3.80)

No class of tocolytic was significantly superior to placebo in reducing neonatal respiratory distress syndrome.

Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012;345:e6226.

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Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Brown J, Medley N, Dalziel SR

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Background

Respiratory morbidity including respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal mortality and disability.

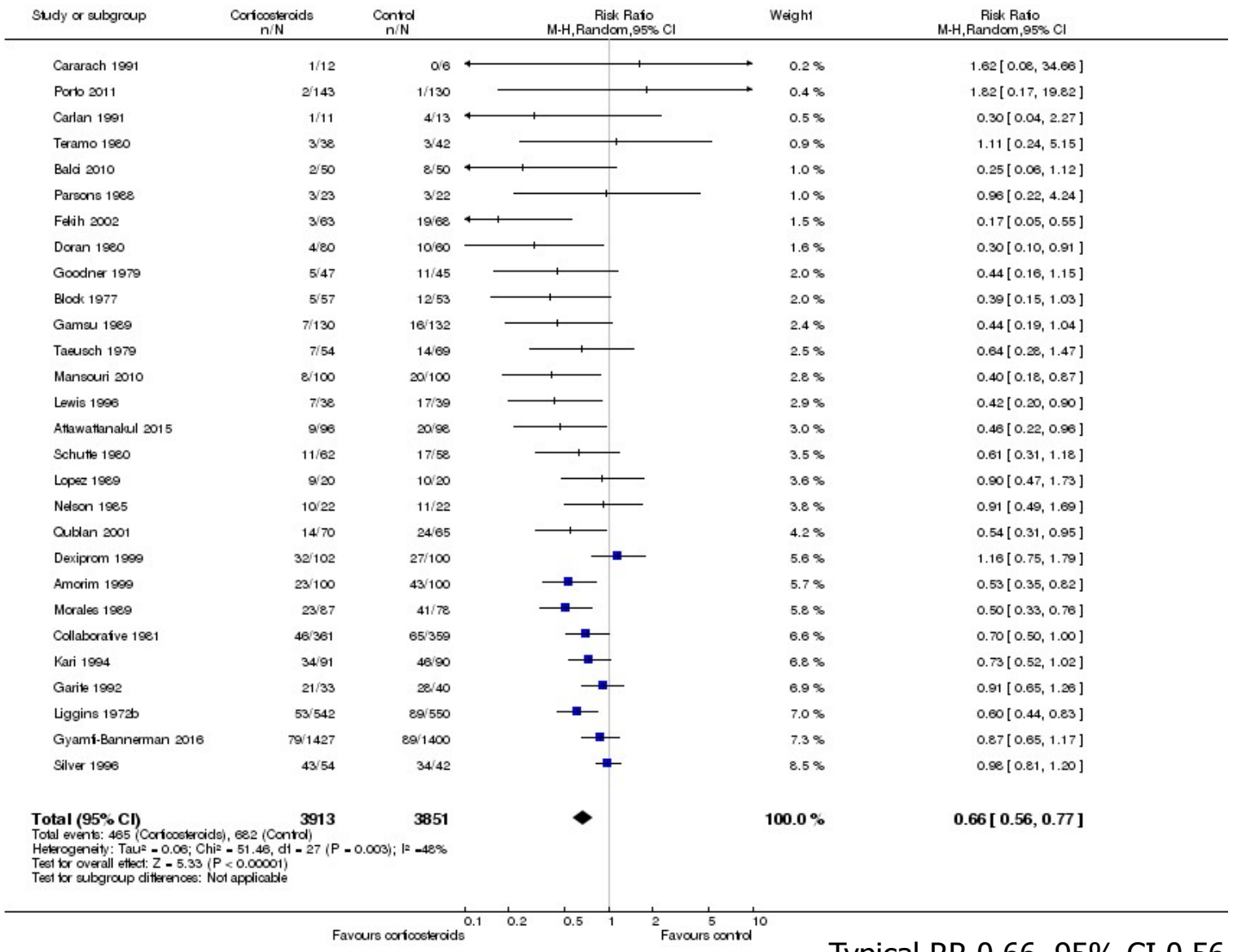
While researching the effects of the steroid dexamethasone on premature parturition in fetal sheep in 1969, Liggins found that there was some inflation of the lungs of lambs born at gestations at which the lungs would be expected to be airless. Liggins and Howie published the first randomized controlled trial in humans in 1972 and many others followed.

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

This update includes 30 studies
(7774 women and 8158 infants).

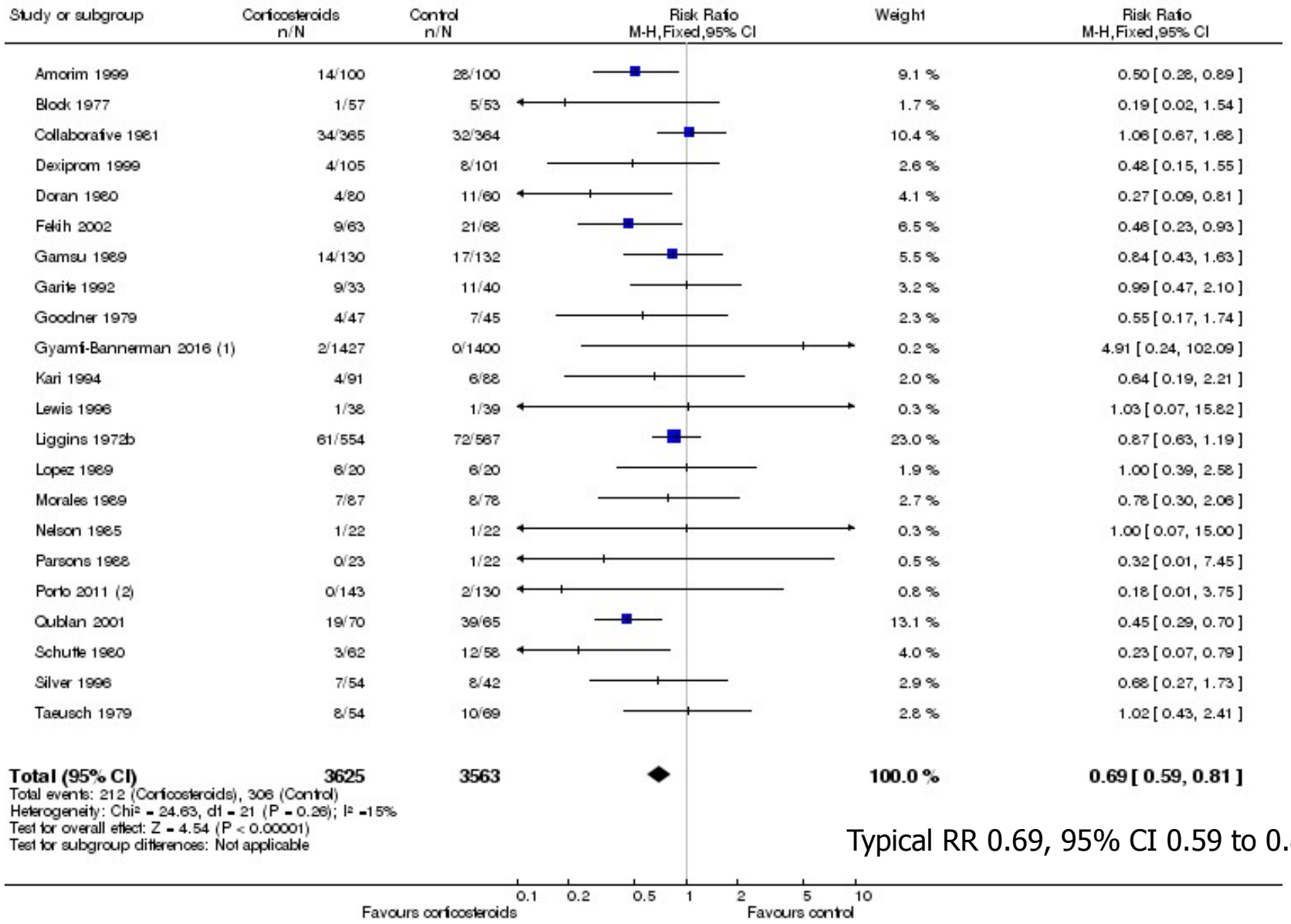
Risk of bias: Most studies are of low or unclear risk for most bias domains.

Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at risk of Preterm Birth: Effect on RDS



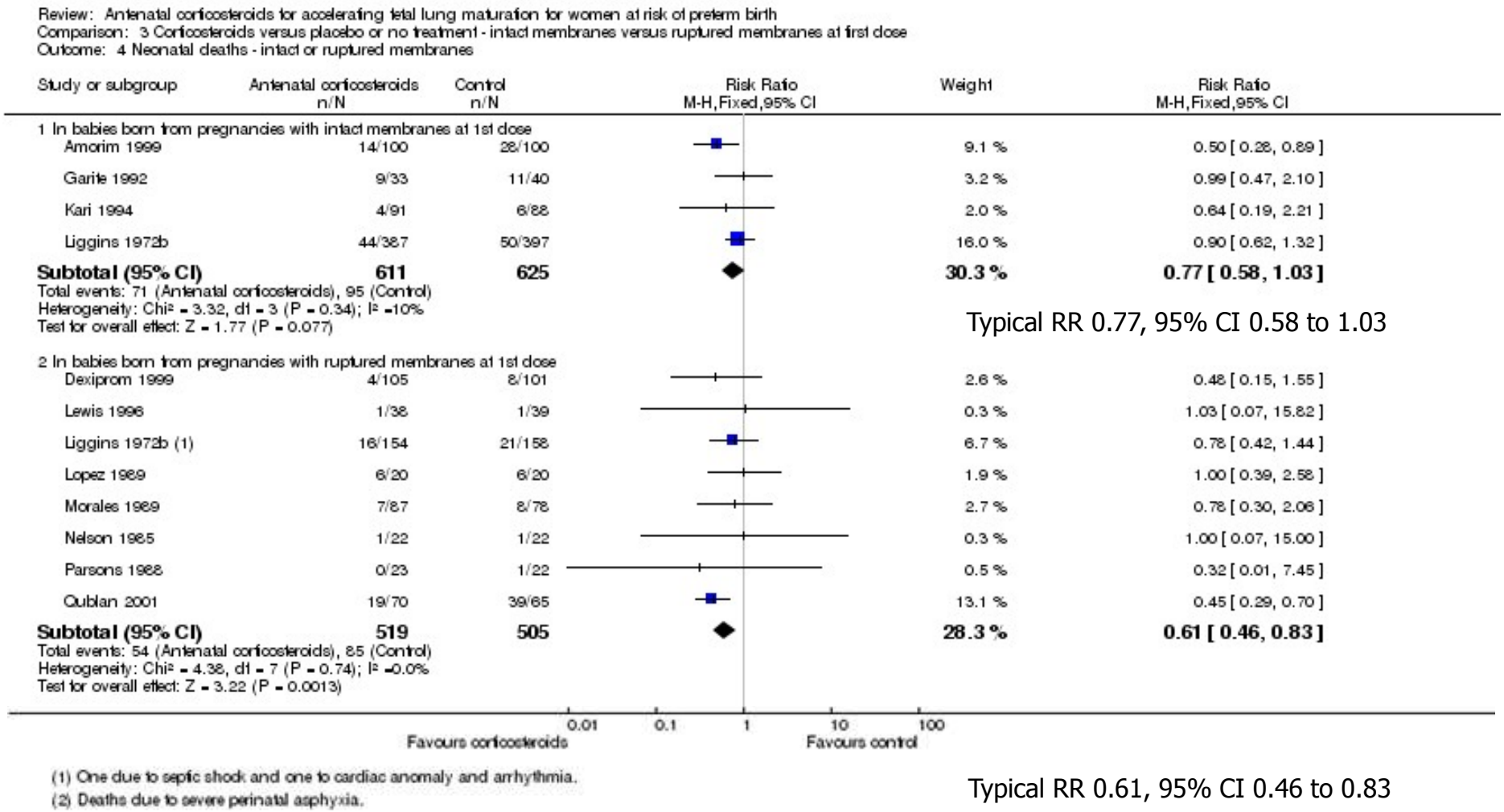
Typical RR 0.66, 95% CI 0.56 to 0.77

Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at risk of Preterm Birth: Effect on Neonatal Death



Typical RR 0.69, 95% CI 0.59 to 0.81

Antenatal Corticosteroids for Accelerating Fetal Lung Maturation for Women at risk of Preterm Birth: Effect on Neonatal Death based on intact or ruptured membranes



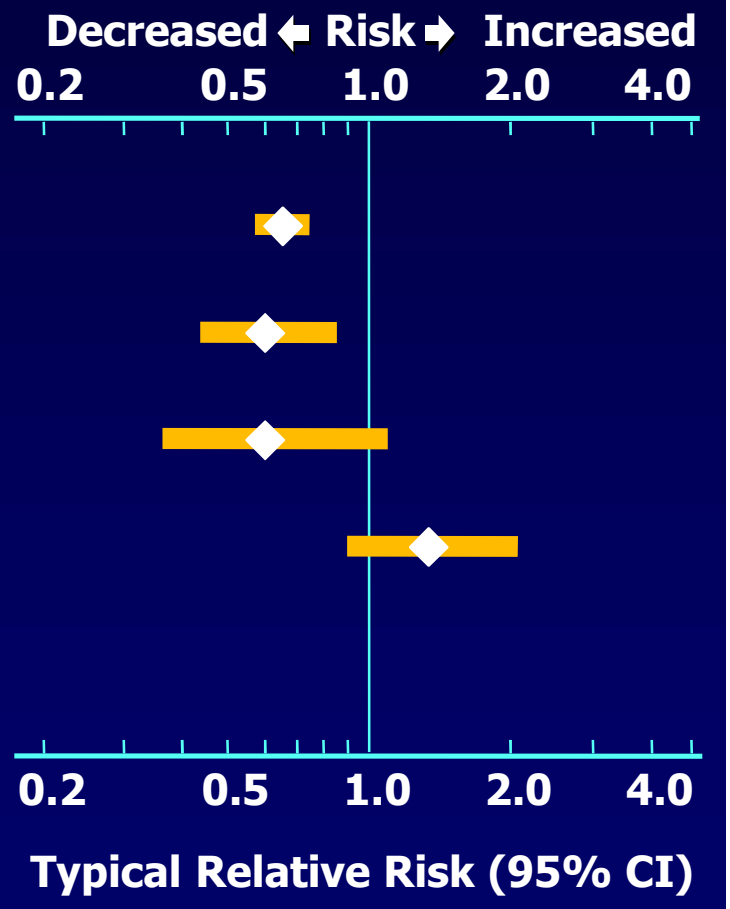
Typical RR 0.77, 95% CI 0.58 to 1.03

Typical RR 0.61, 95% CI 0.46 to 0.83

PROPHYLACTIC CORTICOSTEROIDS PRIOR TO PRETERM BIRTH

OVERVIEW OF 30 RANDOMIZED CONTROLLED TRIALS

Outcome (# of trials)	Typical Relative Risk (95% CI)
Perinatal Death (15)	0.72 (0.58, 0.89)
Chorioamnionitis (15)	0.83 (0.66, 1.06)
Endometritis (10)	1.20 (0.87, 1.63)
Neurodevelopmental delay (1)	0.64 (0.14, 2.98)

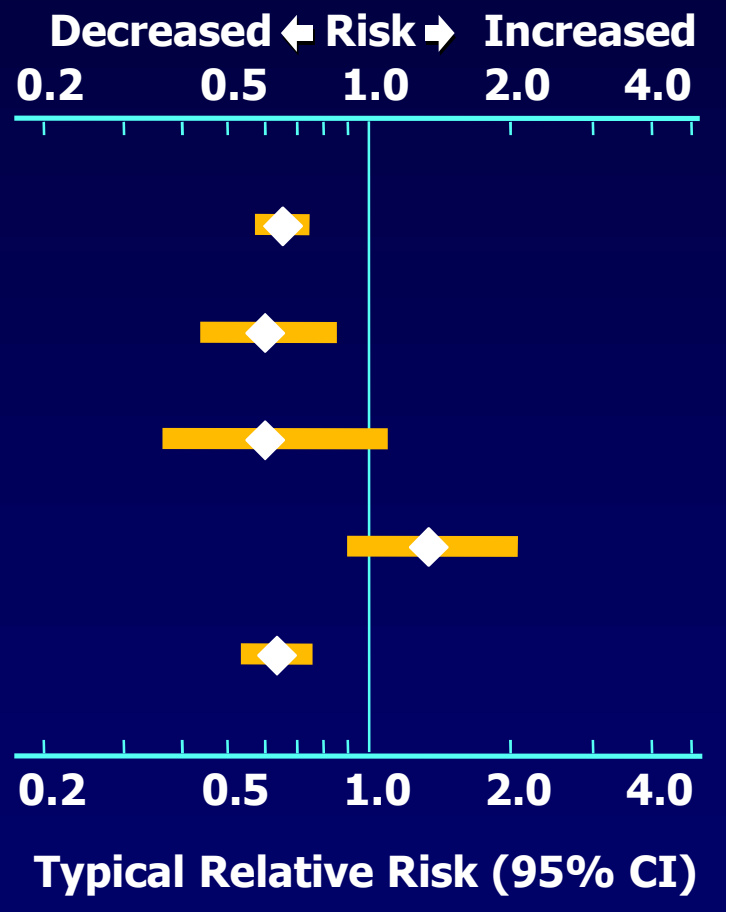


Roberts 2017

PROPHYLACTIC CORTICOSTEROIDS PRIOR TO PRETERM BIRTH

OVERVIEW OF 30 RANDOMIZED CONTROLLED TRIALS

Outcome (# of trials)	Typical Relative Risk (95% CI)
RDS (28)	0.66 (0.56, 0.77)
Intraventricular hemorrhage (16)	0.55 (0.40, 0.76)
Necrotizing enterocolitis (10)	0.50 (0.32, 0.78)
Bronchopulmonary dysplasia (6)	0.86 (0.42, 1.79)
Neonatal death (22)	0.69 (0.59, 0.81)



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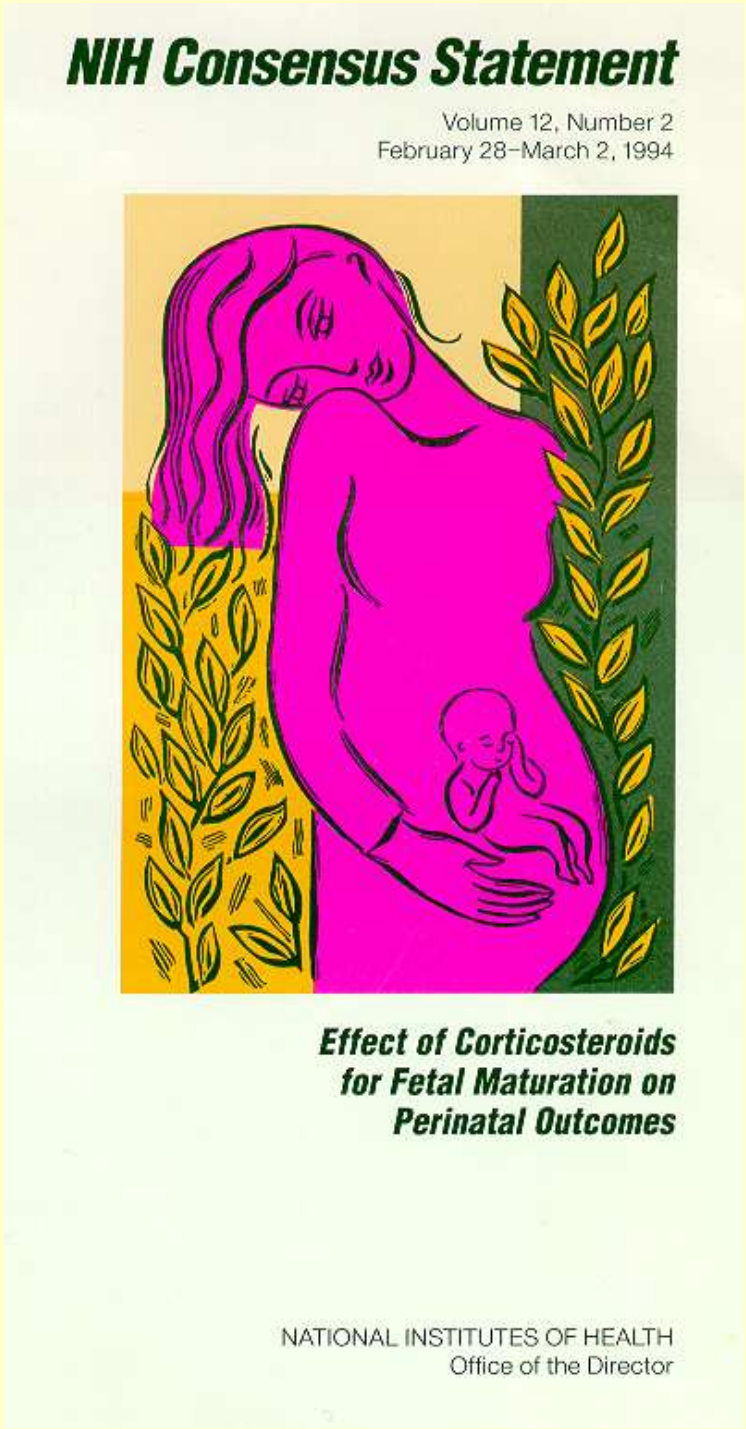
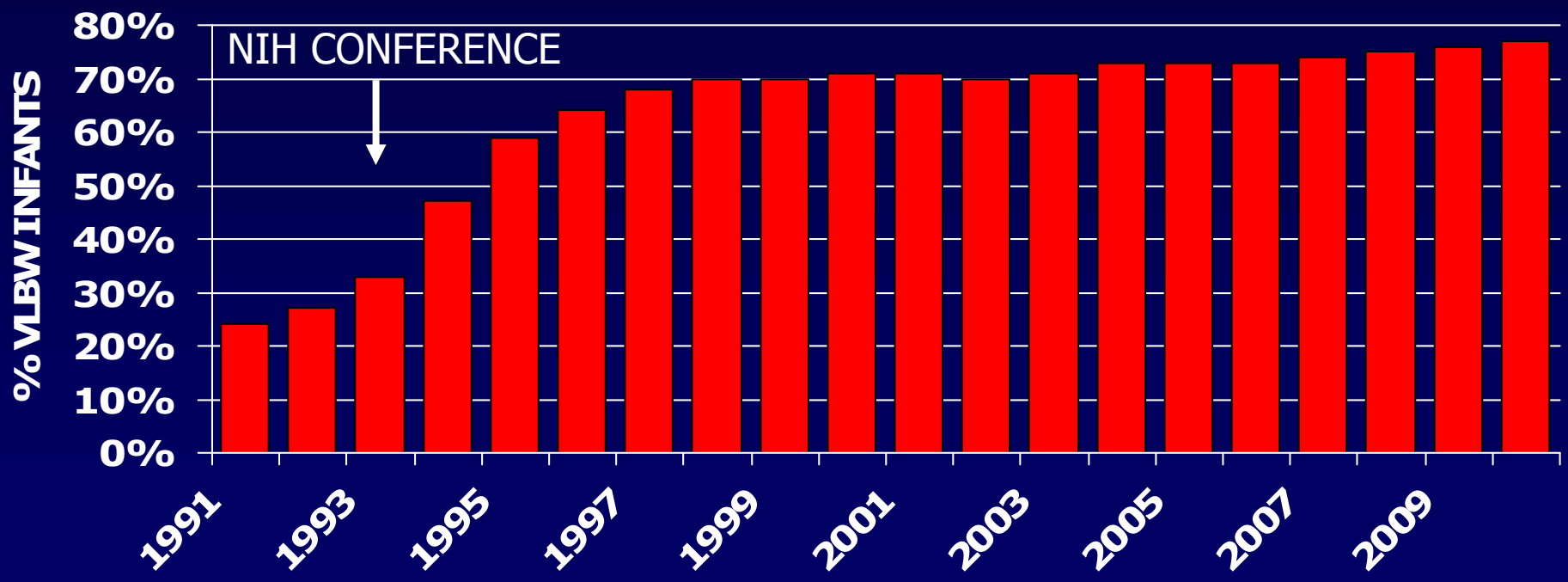


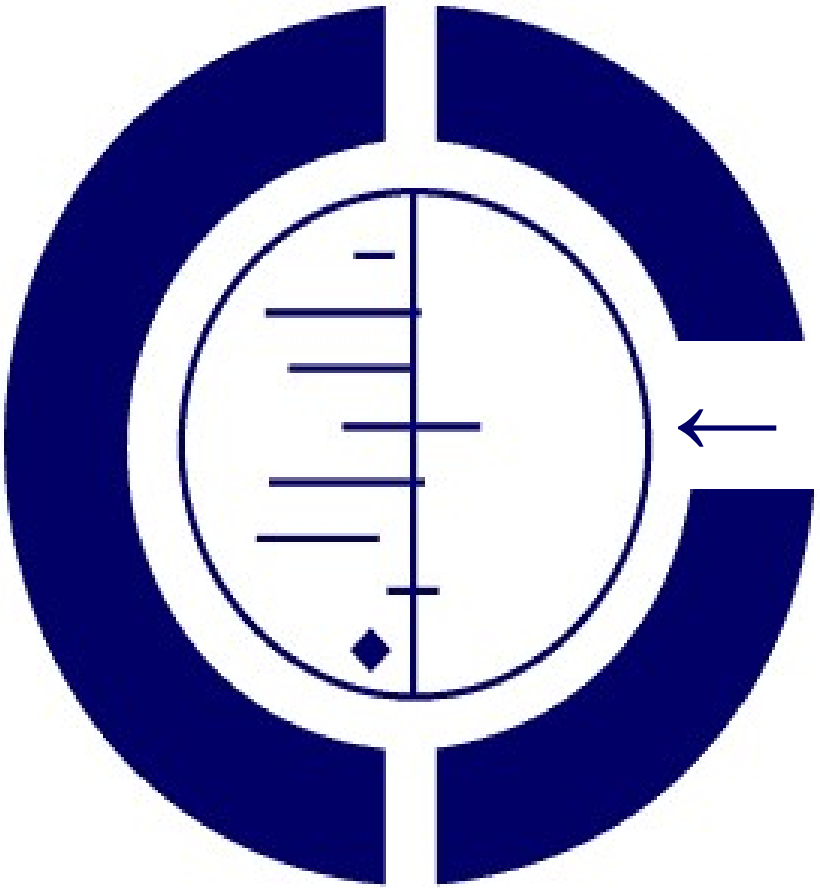
CORTICOSTEROIDS FOR PRETERM BIRTH

"Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs"

ANTENATAL CORTICOSTEROIDS

VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2010





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Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

Crowther CA, McKinlay CJD, Middleton P, Harding JE

Crowther CA, McKinlay CJD, Middleton P, Harding JE.
Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD003935.
DOI: 10.1002/14651858.CD003935.pub4.

Repeat doses of prenatal corticosteroids for women at risk of preterm birth

Types of participants

Women considered to be at risk of preterm birth who have already received a single course of prenatal corticosteroid seven or more days previously.

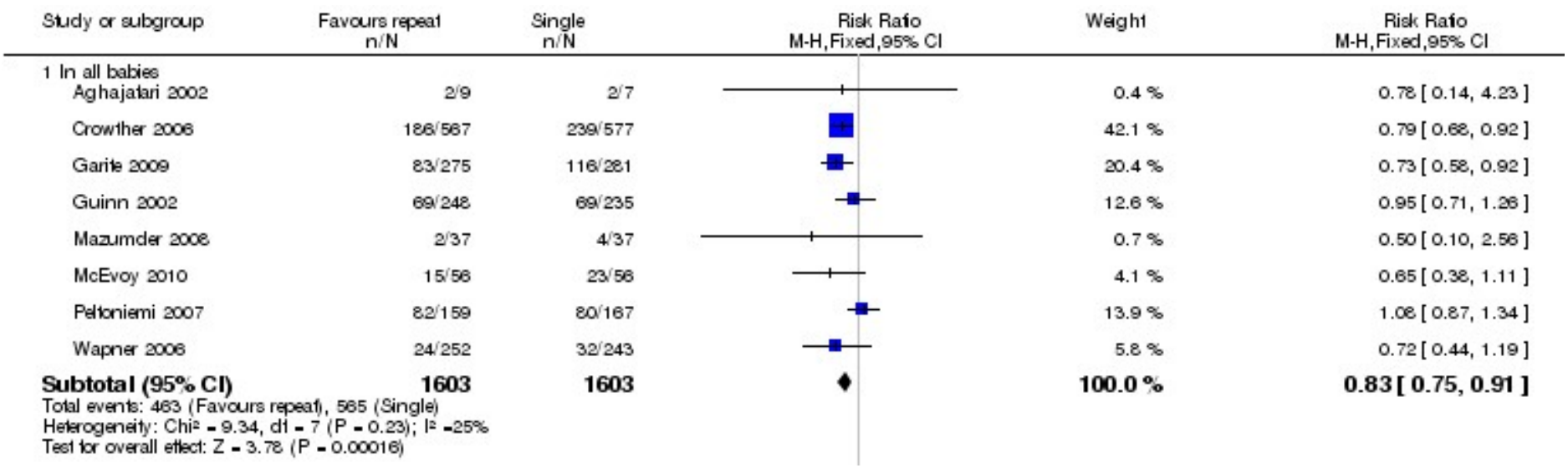
Predefined subgroups were planned to examine separately the outcomes for women and infants based on the reasons the woman was considered to be at risk for preterm birth (e.g. presence or absence of ruptured membranes, antepartum hemorrhage, preterm labor, cervical incompetence, pre-eclampsia, growth restriction), and the number of infants in utero (singleton, twin or higher order multiple pregnancy).

Repeat doses of prenatal corticosteroids for women at risk of preterm birth

This review of 10 randomized controlled trials, involving 4733 women who remained at risk of early birth more than seven days after an initial course of corticosteroids and 5700 babies between 23 and 34 weeks' gestation at trial enrollment.

Repeat doses of prenatal corticosteroids for women at risk of preterm birth

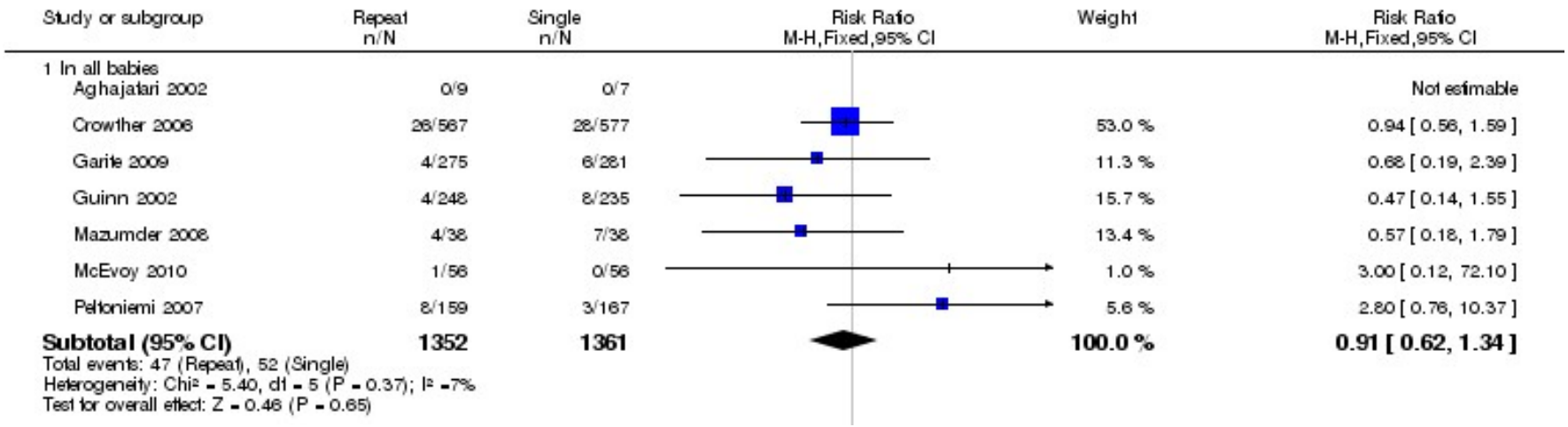
Effect on respiratory distress syndrome



Typical RR 0.83, 95% CI 0.75 to 0.91

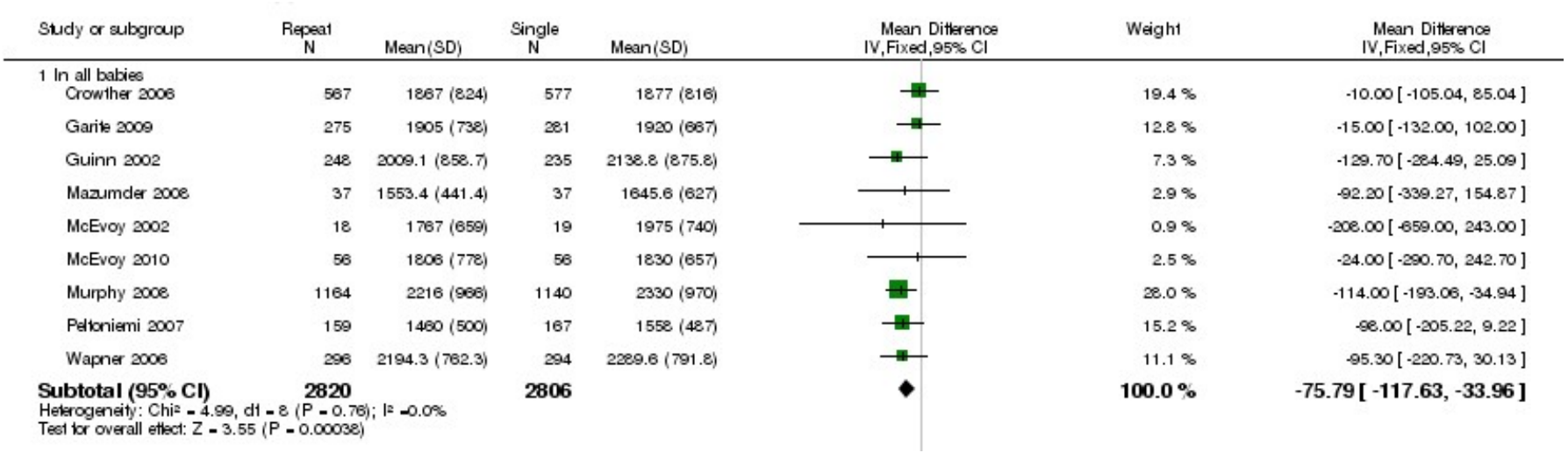
Repeat doses of prenatal corticosteroids for women at risk of preterm birth

Effect on neonatal death

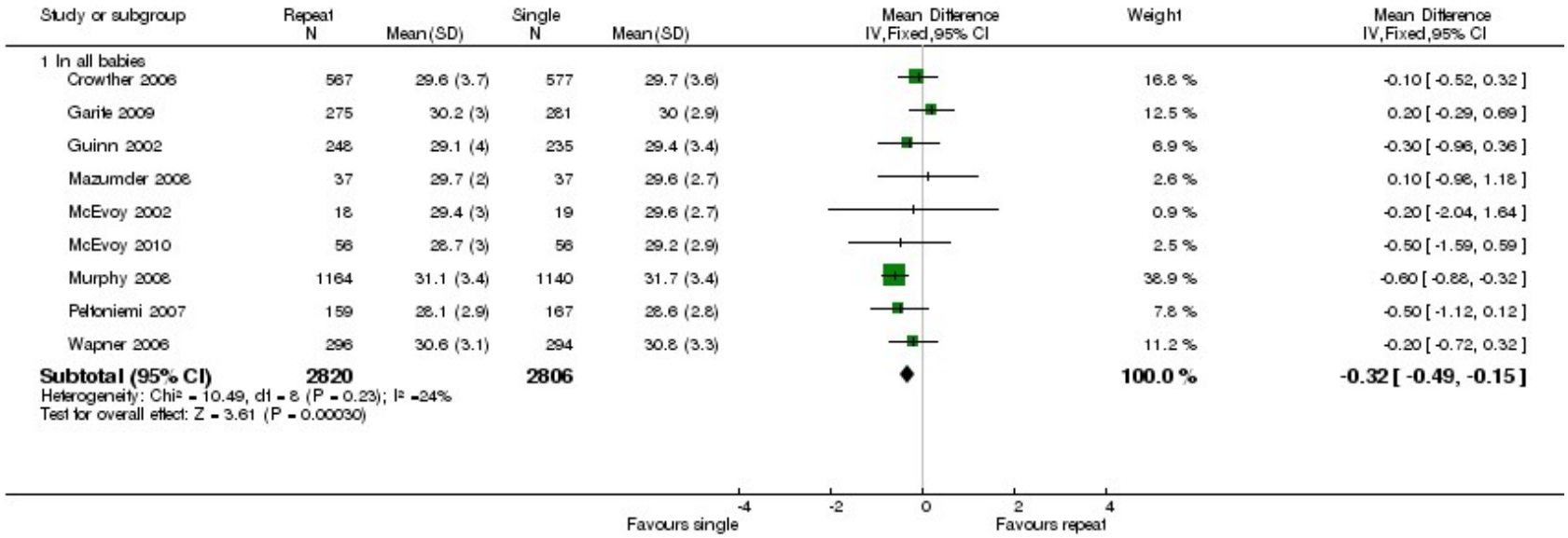


Typical RR 0.91, 95% CI 0.62 to 1.34

Repeat doses of prenatal corticosteroids for women at risk of preterm birth



mean difference in birth weight (MD) -75.79 g, 95% CI -117.63 to -33.96, nine trials, 5626 infants



mean difference in head circumference (MD) -32 cm, 95% CI -49 cm to -15 cm, nine trials, 5626 infants

Repeat doses of prenatal corticosteroids for women at risk of preterm birth

Authors' conclusions:

The short-term benefits for babies of less respiratory distress and fewer serious health problems in the first few weeks after birth support the use of repeat dose(s) of prenatal corticosteroids for women still at risk of preterm birth seven days or more after an initial course. These benefits were associated with a small reduction in size at birth. The current available evidence reassuringly shows no significant harm in early childhood, although no benefit.

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Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity (Review)

Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P, Ota E

Thinkhamrop J, Hofmeyr G, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD002250. DOI: 10.1002/14651858.CD002250.pub3

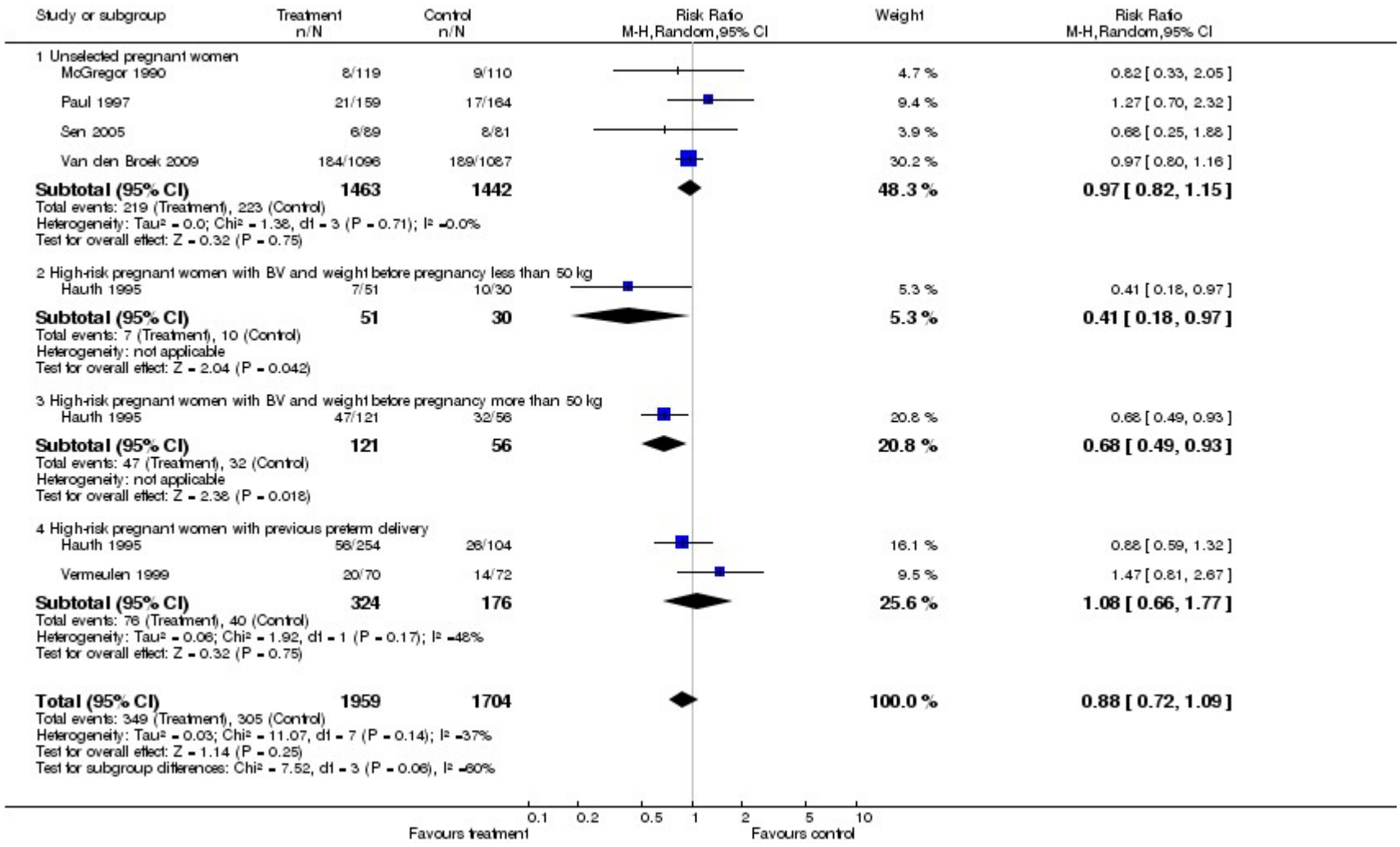
Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity.

Antibiotics are administered to pregnant women during the second and third trimester of pregnancy (before labor) to prevent bacteria in the vagina and cervix affecting the pregnancy.

Infection by some infectious organisms in a woman's genital tract can cause health problems for the mother and her baby, and has been associated with preterm births.

This review of eight randomized trials involved approximately 4300 women in their second or third trimester.

Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity: Effect on preterm delivery



Typical RR 0.88, 95% CI 0.72 to 1.09

Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity.

Preterm delivery was reduced in pregnant women who had a previous preterm birth and bacterial vaginosis during the current pregnancy.

There was no reduction in preterm delivery in pregnant women with previous preterm birth without bacterial vaginosis during the current pregnancy (two trials).

Postpartum endometritis, or infection of the uterus following birth, was reduced overall (three trials, moderate quality of evidence), as well as in a trial of high-risk women who had a previous preterm birth (one trial, moderate quality of evidence).

No reduction in neonatal illness was observed.

Outcomes of interest were available in trials with high losses to follow-up. We could not estimate the side effects of antibiotics since side effects were rare; however, antibiotics may still have serious side effects on women and their babies.

There is, therefore, no justification to give antibiotics to all pregnant women during the second or third trimester to prevent adverse infectious effects on pregnancy outcomes.

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Cochrane Database of Systematic Reviews

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Review)

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D.
Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus.
Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD004661.
DOI: 10.1002/14651858.CD004661.pub3.

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Background:

Epidemiological and basic science evidence suggests that magnesium sulfate before birth may be neuroprotective for the fetus.

Objectives:

To assess the effects of magnesium sulfate as a neuroprotective agent when given to women considered at risk of preterm birth.

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Five trials (6145 babies) were eligible for this review.

Antenatal magnesium sulfate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (relative risk (RR) 0.68; 95% Confidence Interval (CI) 0.54 to 0.87; five trials; 6145 infants).

There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants).

No statistically significant effect of antenatal magnesium sulfate therapy was detected on pediatric mortality (RR 1.04; 95% CI 0.92 to 1.17; five trials; 6145 infants) or on other neurological impairments or disabilities in the first few years of life.

Overall there were no significant effects of antenatal magnesium therapy on combined rates of mortality with cerebral palsy, although there were significant reductions for the neuroprotective groups RR 0.85; 95% CI 0.74 to 0.98; four trials; 4446 infants, but not for the other intent subgroups.

There were higher rates of minor maternal side effects in the magnesium groups, but no significant effects on major maternal complications.

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Authors' conclusions

The neuroprotective role for antenatal magnesium sulfate therapy given to women at risk of preterm birth for the preterm fetus is now established.

The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155).

Given the beneficial effects of magnesium sulfate on substantial gross motor function in early childhood, outcomes later in childhood should be evaluated to determine the presence or absence of later potentially important neurological effects, particularly on motor or cognitive function.

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

COMMITTEE OPINION

Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection

Numerous large clinical studies have evaluated the evidence regarding magnesium sulfate, neuroprotection, and preterm births.

The Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine recognize that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants.

Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials.

OUR CHANGING PRACTICE…
IS IT EVIDENCE BASED?
Cesarean Section

Malloy MH. Impact of cesarean section on neonatal mortality rates among very preterm infants in the United States, 2000-2003. Pediatrics. 2008 Aug;122(2):285-92.

OBJECTIVE: To compare the neonatal mortality rates for infants delivered through primary cesarean section versus vaginal delivery, taking into consideration a number of potentially risk-modifying conditions.

OUR CHANGING PRACTICE…
IS IT EVIDENCE BASED?
Cesarean Section

Demographic, medical, and labor and delivery complications were abstracted from US linked birth and infant death certificate files for 2000-2003.

13,733 neonatal deaths and 106,809 survivors available from the trimmed data set for analysis for the 4-year period.

Malloy MH. Pediatrics. 2008

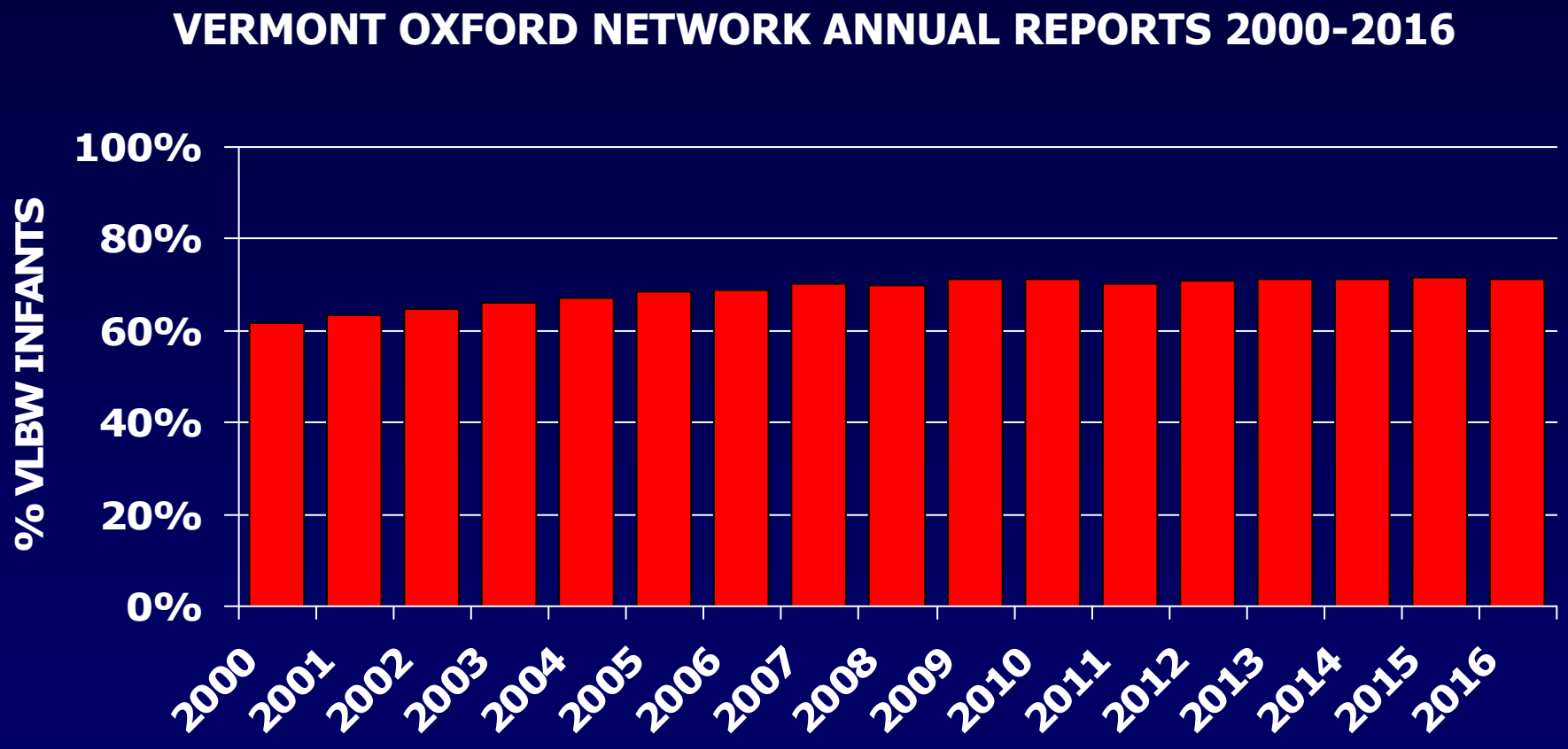
OUR CHANGING PRACTICE…
IS IT EVIDENCE BASED?
Cesarean Section

RISK OF NEONATAL DEATH:

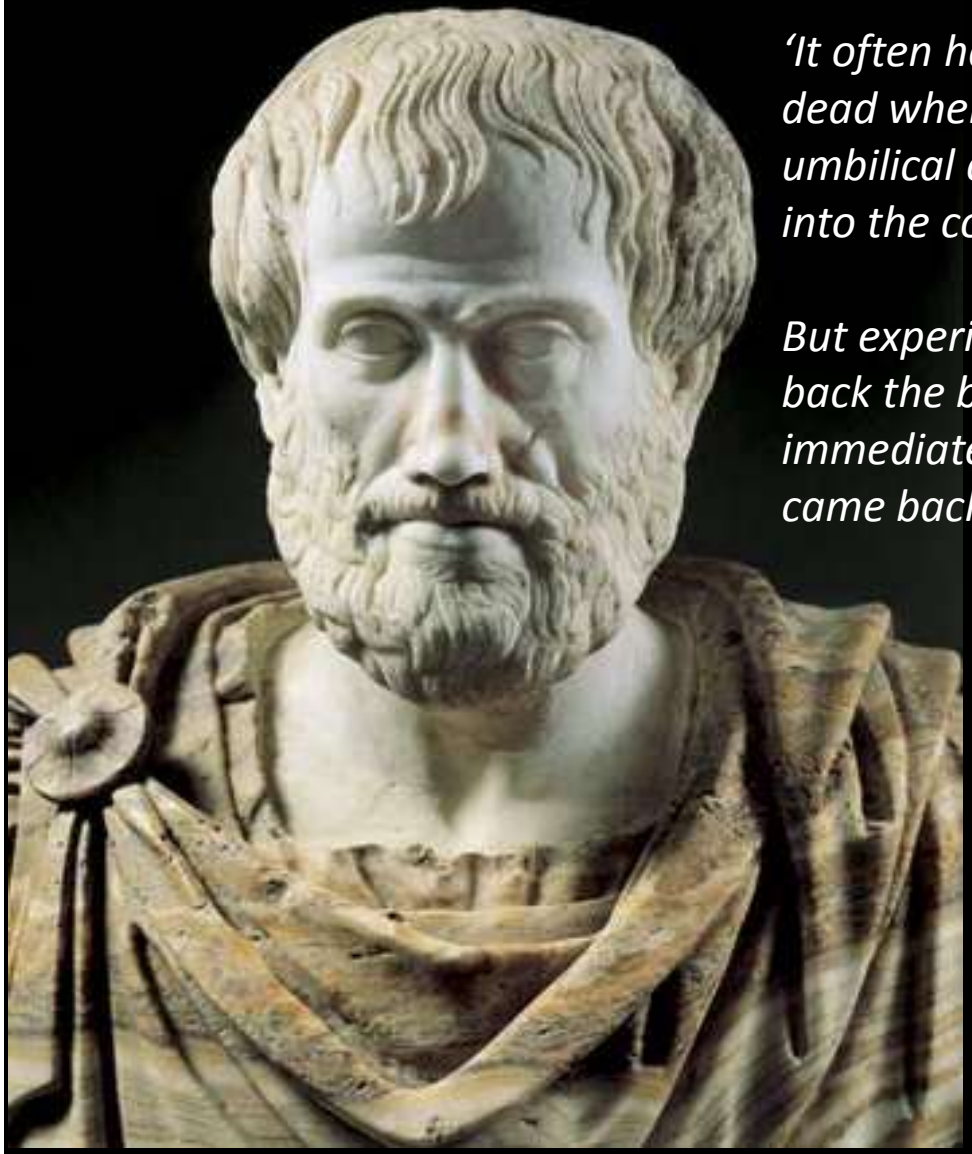
Gestational Age	Adjusted odds ratios and 95% CI
22 weeks	0.58 (0.38–0.87)
23 weeks	0.52 (0.42–0.64)
24 weeks	0.72 (0.62–0.82)
25 weeks	0.81 (0.69–0.94)

Malloy MH. Pediatrics. 2008.

CESARIAN SECTION



Delayed Cord Clamping



'It often happens that the child appears to have been born dead when it is merely weak, and when before the umbilical cord has been ligatured, the blood has run out into the cord and its surroundings.

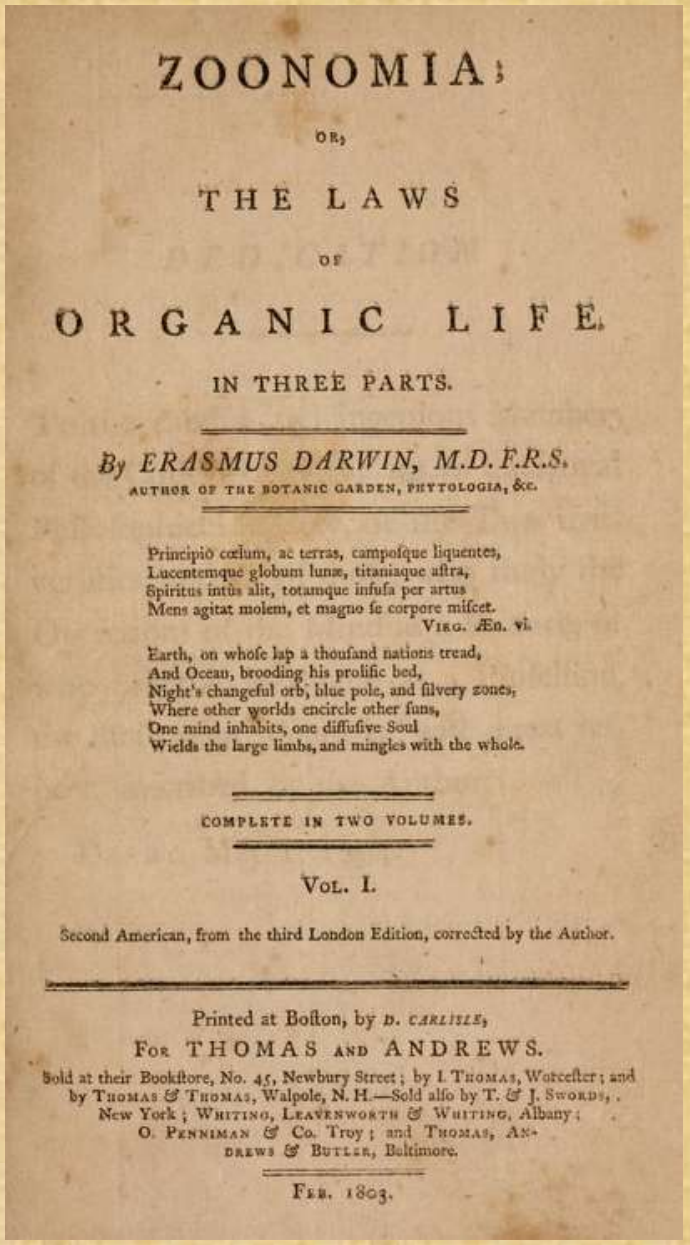
But experienced midwives have been known to squeeze back the blood into the child's body from the cord, and immediately the child that a moment before was bloodless came back to life again.'

Aristotle, ~350 BC.

“Another thing very injurious to the child,
is the tying and cutting of the navel string too soon
which should always be left not only until the child
has repeatedly breathed, but till all pulsations in
the cord cease.

As otherwise the child is much weaker than it
ought to be, a portion of the blood being left in
the placenta, which ought to have been in the
child.“

Erasmus Darwin 1801



ZOONOMIA;

OR,

THE LAWS

OF

ORGANIC LIFE.

IN THREE PARTS.

By ERASMUS DARWIN, M.D. F.R.S.

AUTHOR OF THE BOTANIC GARDEN, PHYTOLOGIA, &c.

Principiò cœlum, ac terras, camposque liquentes,
Lucentemque globum lunæ, titaniaque astra,
Spiritus intùs alit, totamque infusa per artus
Mens agitat molem, et magno se corpore miscet.
VIRG. Æn. vi.

Earth, on whose lap a thousand nations tread,
And Ocean, brooding his prolific bed,
Night's changeful orb, blue pole, and silvery zones,
Where other worlds encircle other suns,
One mind inhabits, one diffusive Soul
Wields the large limbs, and mingles with the whole.

COMPLETE IN TWO VOLUMES.

VOL. I.

Second American, from the third London Edition, corrected by the Author.

Printed at Boston, by D. CARLISLE,
FOR THOMAS AND ANDREWS.
Sold at their Bookstore, No. 45, Newbury Street; by I. THOMAS, Worcester; and by THOMAS & THOMAS, Walpole, N. H.—Sold also by T. & J. SWORDS, New York; WHITING, LEAVENWORTH & WHITING, Albany; O. PENNIMAN & Co. Troy; and THOMAS, ANDREWS & BUTLER, Baltimore.
FEB. 1803.

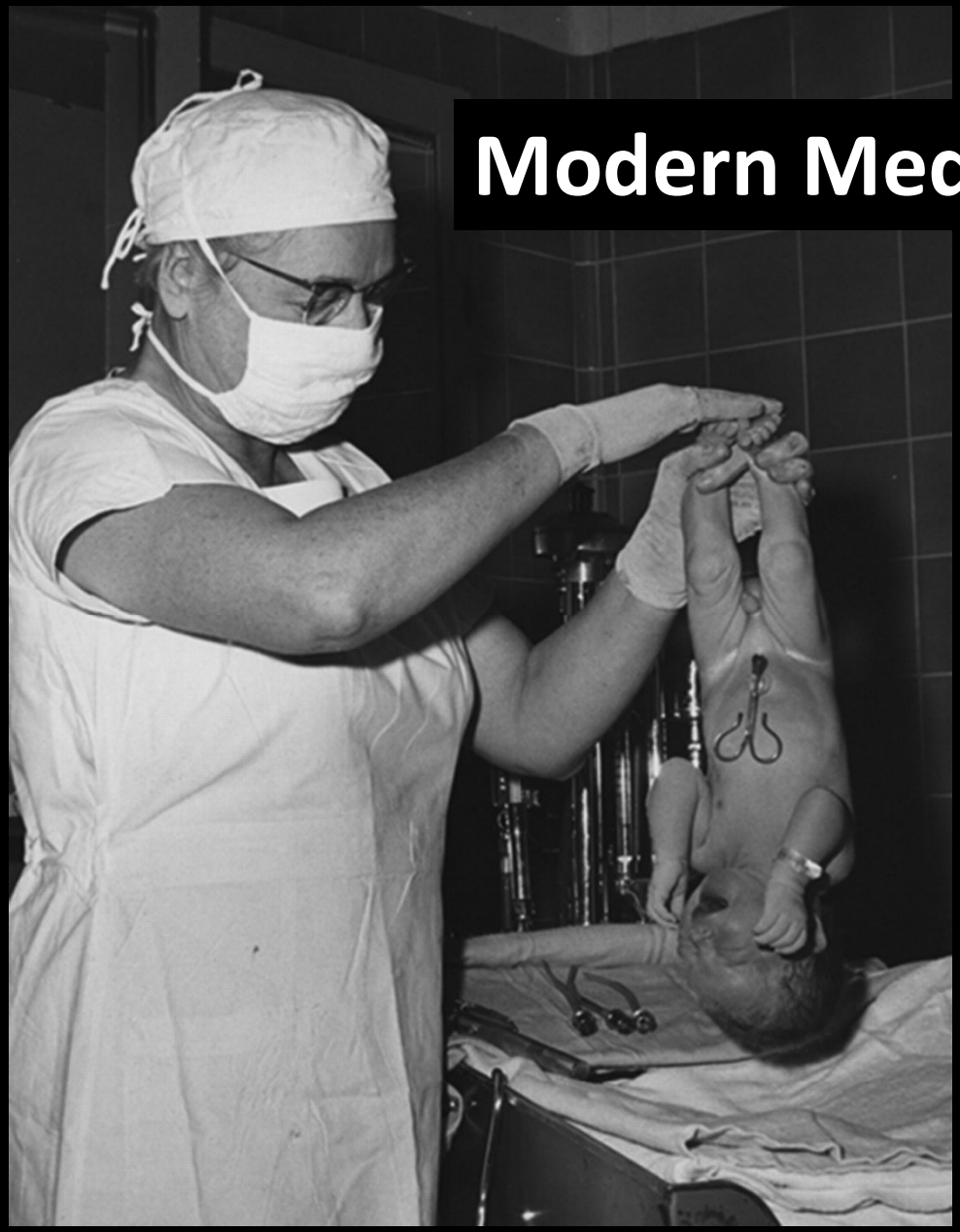
So where does the concept of “early” (read “immediate”) cord clamping come from?

Before the mid 1950s, the term *early clamping* was defined as umbilical cord clamping within 1 minute of birth, and *late clamping* was defined as umbilical cord clamping more than 5 minutes after birth.

In a series of small studies of blood volume changes after birth, it was reported that 80 to 100 mL of blood transfers from the placenta to the newborn in the first 3 minutes after birth and up to 90% of that blood volume transfer was achieved within the first few breaths in healthy term infants (Yao 1969).

Because of these early observations and the lack of specific recommendations regarding optimal timing, the interval between birth and umbilical cord clamping began to be shortened, and it became common practice to clamp the umbilical cord shortly after birth, usually within 15 to 20 seconds.

ACOG COMMITTEE OPINION. Delayed Umbilical Cord Clamping After Birth. Number 684, January 2017



Modern Medicine at it's best!

Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes.

Rabe H, Diaz-Rossello JL, Duley L, Dowswell T.

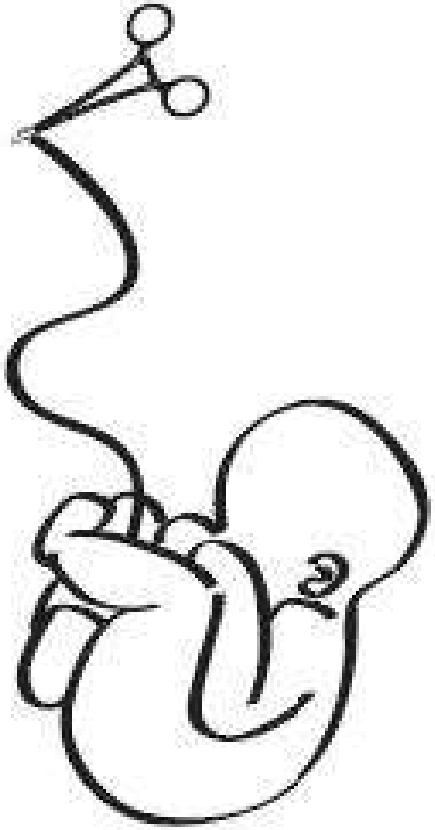
THE COCHRANE COLLABORATION®

How does the APTS Study help further inform our decision?

60 seconds

APTS

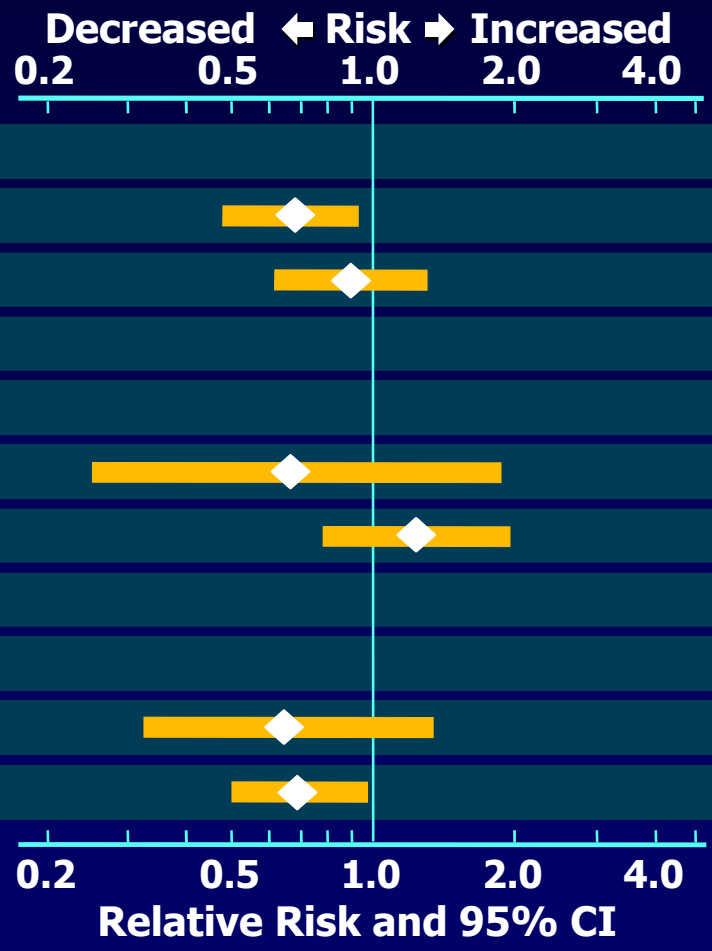
Australian Placental Transfusion Study



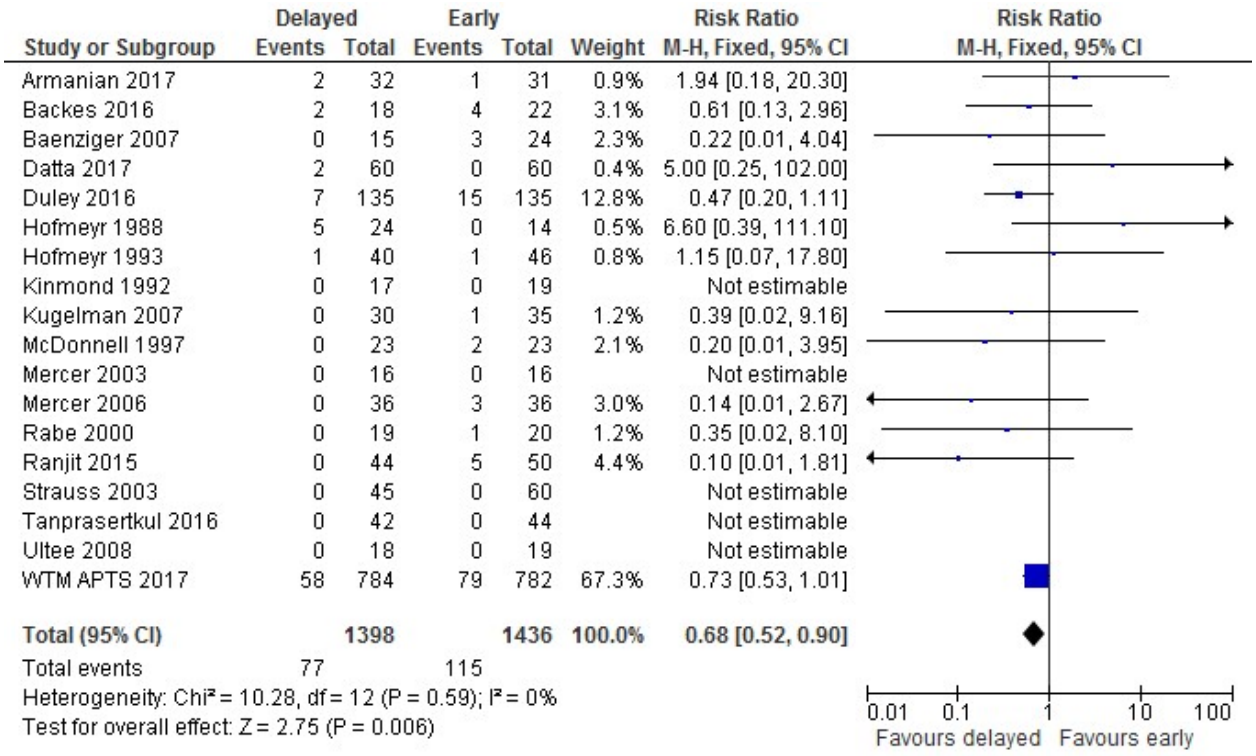
Delayed Cord Clamping

Estimates from Previous Trials and The Australian Placental Transfusion Trial

Outcome	Relative Risk (95% CI)
Necrotizing Enterocolitis	
- Meta-analysis (5)	0.62 (0.43-0.90)
- APTS (1)	0.91 (0.60-1.37)
Severe Intraventricular Hemorrhage	
- Meta-analysis (6)	0.68 (0.23-1.96)
- APTS (1)	1.35 (0.73-2.48)
Mortality	
- Meta-analysis (13)	0.63 (0.31-1.28)
- APTS (1)	0.69 (0.49-0.97)



Delayed versus early cord clamping in preterm infants
Effect on Mortality (NEW ANALYSIS) Relative Risk



Study or Subgroup	Delayed Events	Delayed Total	Early Events	Early Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2017	2	32	1	31	0.9%	1.94 [0.18, 20.30]
Backes 2016	2	18	4	22	3.1%	0.61 [0.13, 2.96]
Baenziger 2007	0	15	3	24	2.3%	0.22 [0.01, 4.04]
Datta 2017	2	60	0	60	0.4%	5.00 [0.25, 102.00]
Duley 2016	7	135	15	135	12.8%	0.47 [0.20, 1.11]
Hofmeyr 1988	5	24	0	14	0.5%	6.60 [0.39, 111.10]
Hofmeyr 1993	1	40	1	46	0.8%	1.15 [0.07, 17.80]
Kinmond 1992	0	17	0	19		Not estimable
Kugelman 2007	0	30	1	35	1.2%	0.39 [0.02, 9.16]
McDonnell 1997	0	23	2	23	2.1%	0.20 [0.01, 3.95]
Mercer 2003	0	16	0	16		Not estimable
Mercer 2006	0	36	3	36	3.0%	0.14 [0.01, 2.67]
Rabe 2000	0	19	1	20	1.2%	0.35 [0.02, 8.10]
Ranjit 2015	0	44	5	50	4.4%	0.10 [0.01, 1.81]
Strauss 2003	0	45	0	60		Not estimable
Tanprasertkul 2016	0	42	0	44		Not estimable
Ultee 2008	0	18	0	19		Not estimable
WTM APTS 2017	58	784	79	782	67.3%	0.73 [0.53, 1.01]
Total (95% CI)		**1398**		**1436**	**100.0%**	**0.68 [0.52, 0.90]**
Total events	77		115			

Heterogeneity: Chi² = 10.28, df = 12 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.75 (P = 0.006)

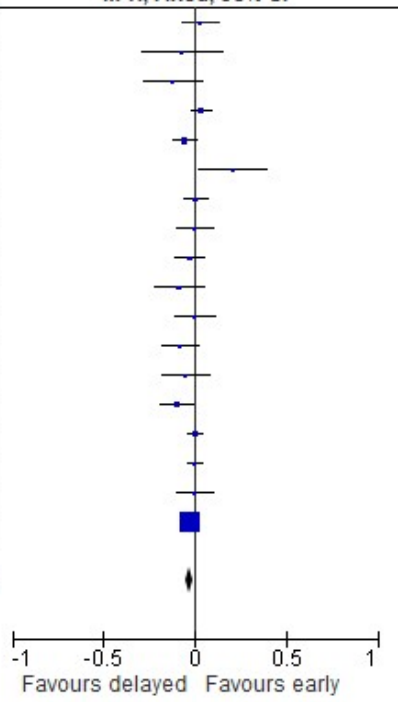
Typical RR 0.68 (95% CI 0.52 to 0.90)

Delayed versus early cord clamping in preterm infants
Effect on Mortality (NEW ANALYSIS) Risk Difference

Study or Subgroup	Delayed Events	Delayed Total	Early Events	Early Total	Weight	Risk Difference M-H, Fixed, 95% CI
Armanian 2017	2	32	1	31	2.2%	0.03 [-0.07, 0.13]
Backes 2016	2	18	4	22	1.4%	-0.07 [-0.29, 0.15]
Baenziger 2007	0	15	3	24	1.3%	-0.13 [-0.29, 0.04]
Datta 2017	2	60	0	60	4.2%	0.03 [-0.02, 0.09]
Duley 2016	7	135	15	135	9.6%	-0.06 [-0.12, 0.01]
Hofmeyr 1988	5	24	0	14	1.3%	0.21 [0.02, 0.39]
Hofmeyr 1993	1	40	1	46	3.0%	0.00 [-0.06, 0.07]
Kinmond 1992	0	17	0	19	1.3%	0.00 [-0.10, 0.10]
Kugelman 2007	0	30	1	35	2.3%	-0.03 [-0.11, 0.05]
McDonnell 1997	0	23	2	23	1.6%	-0.09 [-0.22, 0.05]
Mercer 2003	0	16	0	16	1.1%	0.00 [-0.11, 0.11]
Mercer 2006	0	36	3	36	2.5%	-0.08 [-0.18, 0.02]
Rabe 2000	0	19	1	20	1.4%	-0.05 [-0.18, 0.08]
Ranjit 2015	0	44	5	50	3.3%	-0.10 [-0.19, -0.01]
Strauss 2003	0	45	0	60	3.6%	0.00 [-0.04, 0.04]
Tanprasertkul 2016	0	42	0	44	3.0%	0.00 [-0.04, 0.04]
Ultee 2008	0	18	0	19	1.3%	0.00 [-0.10, 0.10]
WTM APTS 2017	58	784	79	782	55.4%	-0.03 [-0.06, 0.00]
Total (95% CI)		**1398**		**1436**	**100.0%**	**-0.03 [-0.05, -0.01]**
Total events	77		115			

Heterogeneity: Chi² = 24.00, df = 17 (P = 0.12); I² = 29%

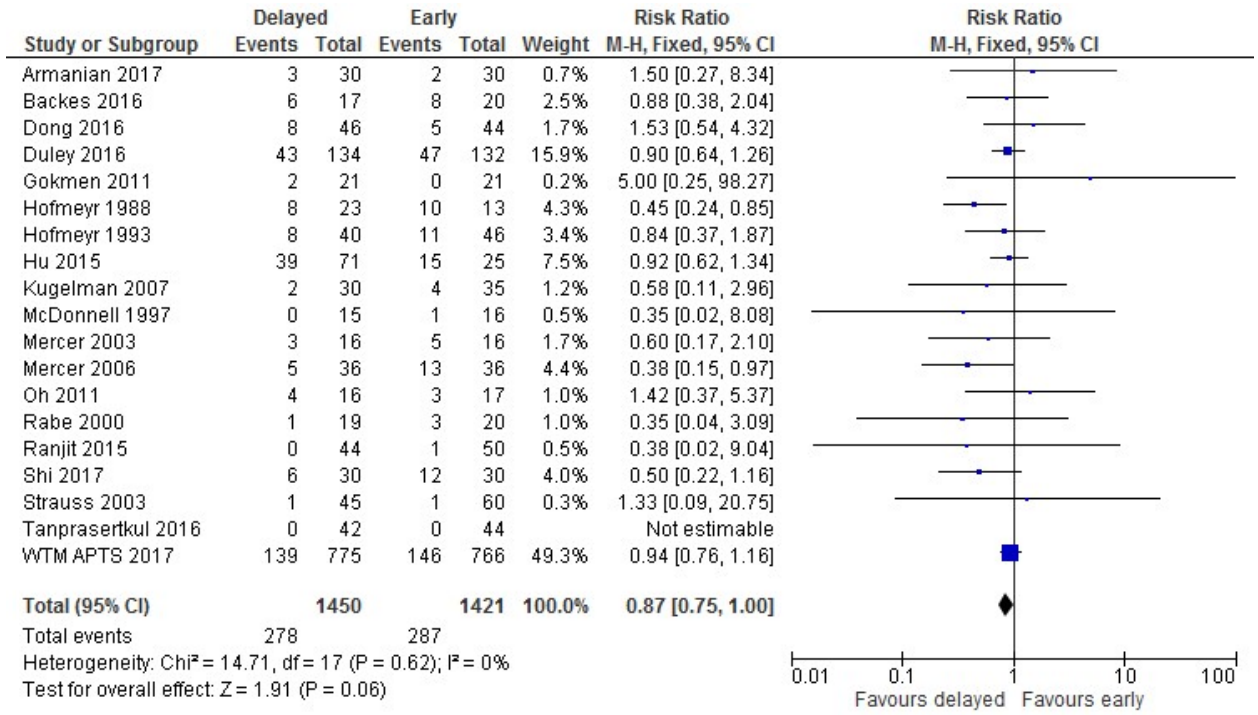
Test for overall effect: Z = 2.79 (P = 0.005)



Typical RD -0.03 (95% CI -0.05 to -0.01)

Delayed versus early cord clamping in preterm infants

Effect on Any Intraventricular Hemorrhage (NEW ANALYSIS) Relative Risk



Typical RR 0.87 (95% CI 0.75 to 1.00)

The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice recommendations regarding the timing of umbilical cord clamping after birth:

In term infants, delayed umbilical cord clamping increases hemoglobin levels at birth and improves iron stores in the first several months of life, which may have a favorable effect on developmental outcomes.

Delayed umbilical cord clamping is associated with significant neonatal benefits in preterm infants, including improved transitional circulation, better establishment of red blood cell volume, decreased need for blood transfusion, and lower incidence of necrotizing enterocolitis and intraventricular hemorrhage.

Given the benefits to most newborns and concordant with other professional organizations, the American College of Obstetricians and Gynecologists now recommends a delay in umbilical cord clamping in vigorous term and preterm infants for at least 30 to 60 seconds after birth.

There is a small increase in the incidence of jaundice that requires phototherapy in term infants undergoing delayed umbilical cord clamping. Consequently, obstetrician–gynecologists and other obstetric care providers adopting delayed umbilical cord clamping in term infants should ensure that mechanisms are in place to monitor and treat neonatal jaundice.

Delayed umbilical cord clamping does not increase the risk of postpartum hemorrhage.

ACOG COMMITTEE OPINION. Delayed Umbilical Cord Clamping After Birth. Number 684, January 2017

Cochrane Neonatal

Guest Discussant

Antenatal Corticosteroids:
Translating the evidence to our smallest and most fragile patients

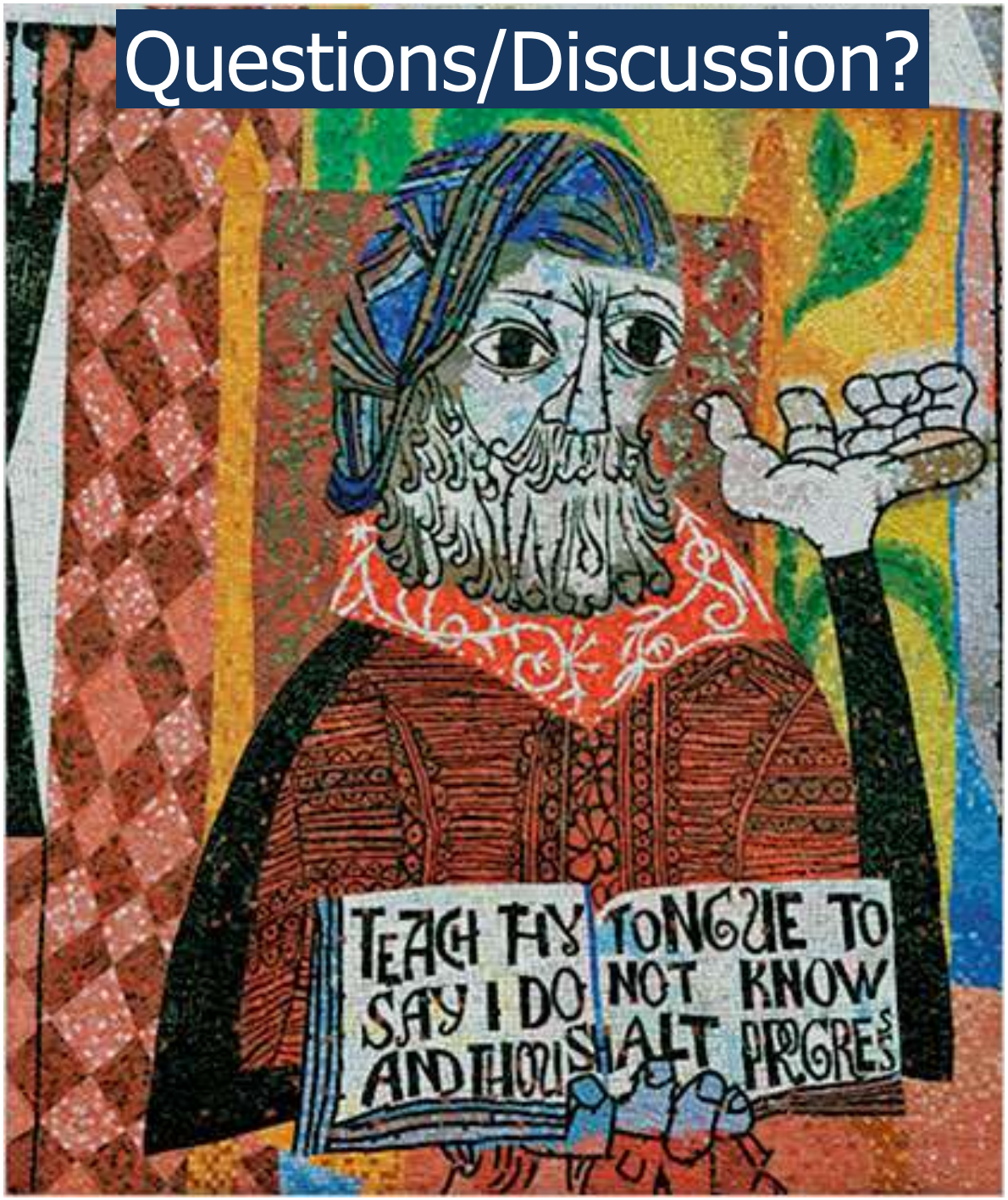
Danielle Ehret, MD, MPH
Assistant Professor of Pediatrics
University of Vermont College of Medicine

Cochrane Neonatal

INSERT VIDEO

Comments from our favorite MFM Specialist!

Questions/Discussion?



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Diagnostic Test Accuracy Fall 2018

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Please contact Jennifer Spano at Jennifer.Spano@med.uvm.edu with questions.