



The use of corticosteroids in pregnancy. Benefits and side effects.

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Financial and Other Disclosures

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No financial relationships	N

Administration of corticosteroids in late preterms. The controversy.

- **History and instructions for administration**
- **Late preterm neonates**
- **Extreme preterm neonates**
- **Elective Cesarean Section**
- **Preterm PROM – Twins**
- **Rescue dose – Repeat doses**
- **Comparison of guidelines**



+History of Steroid Used in Preterm Birth



Graham Liggins



Liggins & Howie

1960

Graham Liggins was investigating factors involved in the initiation of labor in a sheep model. His hypothesis was that the fetus produces substances that trigger labor, possibly steroid hormones. In postmortem analyses, Liggins incidentally found that preterm lambs exposed to corticosteroids had structurally more mature lungs than expected, and were also viable at an earlier gestational age and had less severe respiratory distress at birth.

dr. Aldika Akbar SpOG

1972

Landmark study
A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1970;50:515-25.



Pathways for corticosteroids in lung maturity

Cardiovascular system:

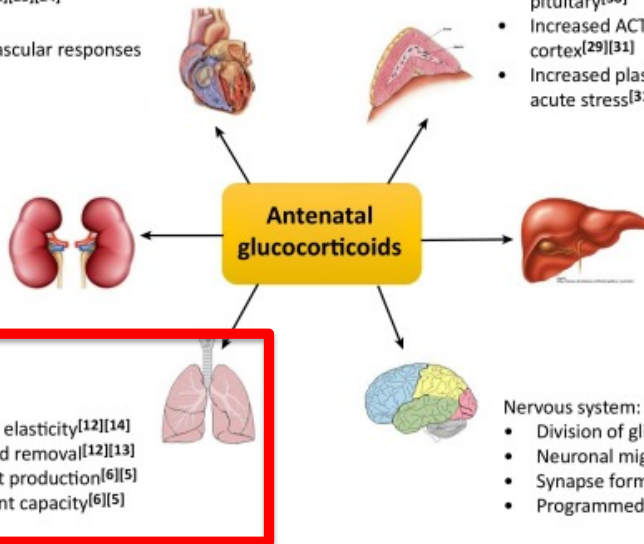
- Increased blood pressure^{[19][20]}
- Increased cardiac contractility^{[2][23][24]}
- Increased cardiac output^[24]
- Altered baroreflex and cardiovascular responses to acute stress^{[21][22][25][27][28]}

Kidneys:

- Decreased fractional excretion of Na⁺ ^{[32][33]}
- Increased GFR^{[33][35]}
- Increased renin production ^{[19][38][39]}
- Decreased nephrogenesis^[37]

Lungs:

- Increased elasticity^{[12][14]}
- Lung liquid removal^{[12][13]}
- Surfactant production^{[6][5]}
- Antioxidant capacity^{[6][5]}



HPA Axis

- Increased POMC production in the pituitary^[30]
- Increased ACTH sensitivity of adrenal cortex^{[29][31]}
- Increased plasma cortisol response to acute stress^[31]

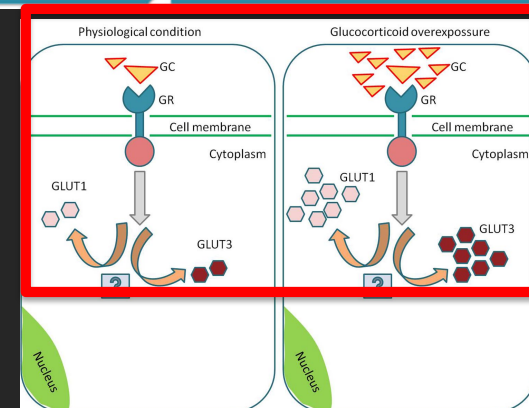
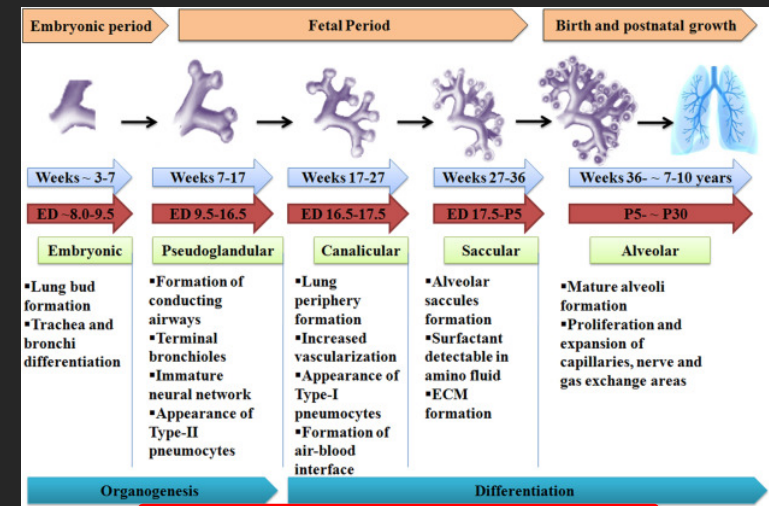
Metabolism:

- Increased gluconeogenic capacity^{[11][49]}
- Production of digestive enzymes ^{[11][49]}
- Switch towards metabolism of fatty acids^{[11][49]}

Nervous system:

- Division of glia and astrocytes^[17]
- Neuronal migration^{[16][17]}
- Synapse formation^{[16][17]}
- Programmed cell death^{[17][18]}

Trends in Endocrinology & Metabolism



The affect of in-utero use of corticosteroids in preterm neonates

- Respiratory distress syndrome (RDS)
- Intraventricular hemorrhage
- Necrotic enterocolitis (NE)
- Perinatal mortality

Betamethasone: 12mg IM in 2 doses with 24 hours difference

Dexamethasone: 6mg IM in 4 doses with 12 hours difference



48 hours



Meta-analysis: corticosteroids and neurodevelopment

Neurodevelopmental Outcome After a Single Course of Antenatal Steroids in Children Born Preterm

^{ad}
A Systematic Review and Meta-analysis

Alexandros Sotiriadis, MD, PhD, Alexandra Tsiami, MD, Stefania Papatheodorou, MD, PhD, Ahmet A. Baschat, MD, PhD, Kosmas Sarafidis, MD, PhD, and George Makrydimas, MD, PhD

Mainly non-randomized trials

Cerebral palsy

RR 0.68

PDI <70

RR 0.83

Severe disability

RR 0.79

Healthy survival

RR 1.18

Neonates born <34 weeks

RCOG guidelines: Corticosteroid Use in Pregnancy 2010

- 24⁺⁰ - 34⁺⁶ wks
- Elective Cesarean Section until 38⁺⁶ wks
- IUGR: 24⁺⁰ - 35⁺⁶ wks
- Repeat dose: only if the first dose <26wks
- Attention: Tuberculosis or inflammatory conditions
- Gestational diabetes: Increased insulin doses

ACOG guidelines for corticosteroid use 2017

- 24⁺⁰ - 33⁺⁶ wks: if delivery is imminent in the next 7 days
- 34⁺⁰ - 36⁺⁶ wks (Late preterm): If childbirth is imminent in the next 7 days and no corticosteroids have been administered until then
- NO in chorioamnionitis, severe preeclampsia & emergency
- Repeat dose <34wks: YES, if childbirth is imminent in the next 7 days and the previous corticosteroid regimen had been given for > 14 days
- Repeat dose in pPROM: Inadequate data

SOGC: Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes 2018

- Administer if **medically indicated delivery planned within 7 days**
- Do **NOT** administer **in absence of cervical dilation/change** or in the **absence of regular contractions**
- Administer at the time of diagnosis of pPROM
- Administer in cases of **significant antepartum hemorrhage** with a high risk of delivery within **7 days**
- Administer in cases of **asymptomatic vasa previa or placenta previa** with a high risk of delivery within **7 days**
- Do **NOT administer rescue dose or course routinely**

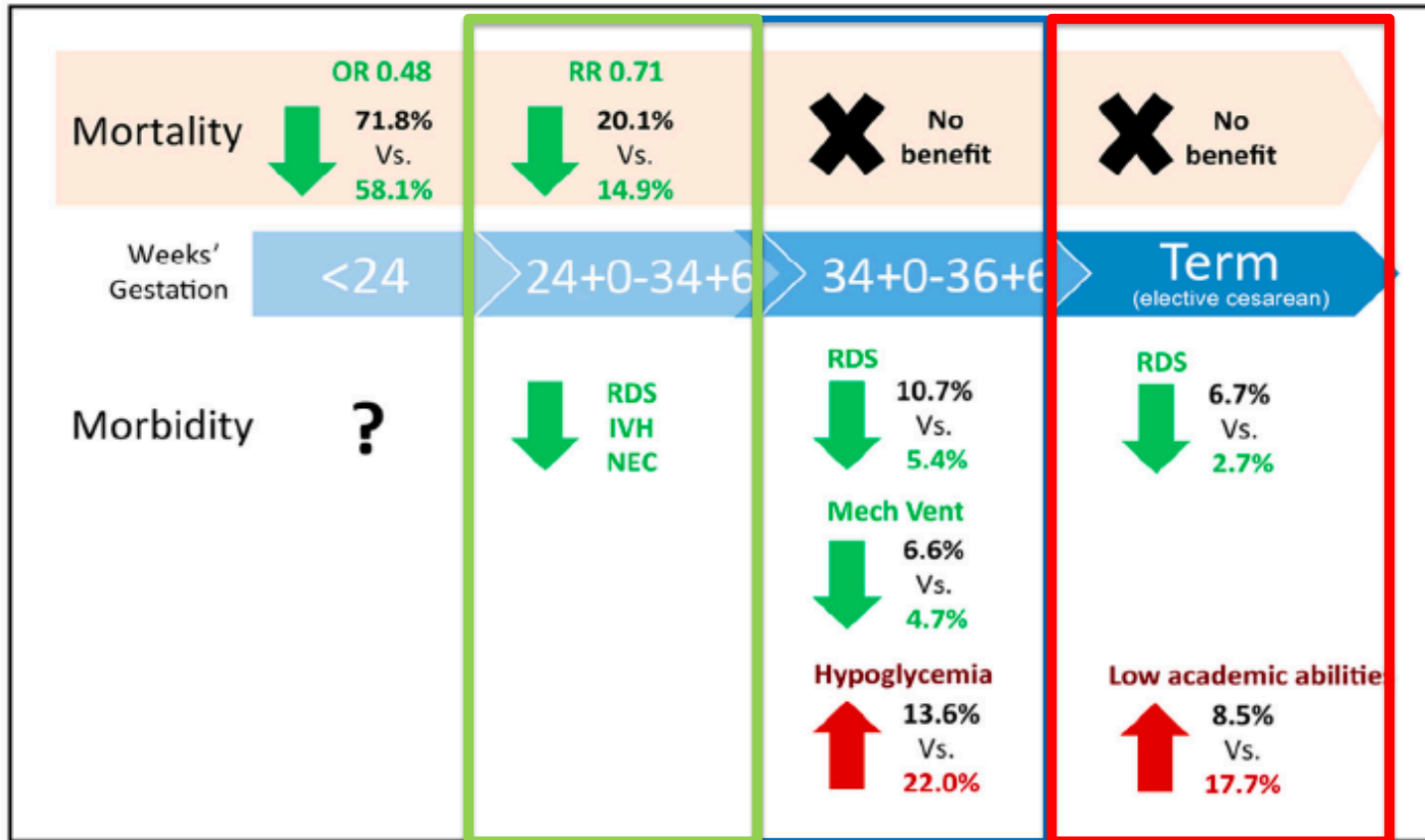
Table 7. Summary table of recommendations for agents, dosage and regimens

Agents, dosage, and regimens	Recommendation when gestational age criteria for antenatal corticosteroid therapy are met	Level of evidence	Strength of recommendation
Agents and dosage	2 × 12 mg doses of betamethasone IM, 24 hours apart or 4 × 6 mg doses of dexamethasone IM, 12 hours apart	Moderate	Strong
Timing of antenatal corticosteroid initiation	Administer if medically indicated delivery planned within 7 days	Low	Strong
	Administer if woman is in spontaneous preterm labour (ie, regular uterine contractions associated with significant cervical dilation or significant cervical change on repeated examination)	Low	Strong
	Do not administer in absence of cervical dilation/change or in the absence of regular contractions	Low	Strong
	Administer at the time of diagnosis of preterm premature rupture of membranes	Low	Strong
	Administer in cases of significant antepartum hemorrhage with a high risk of delivery within 7 days	Low	Strong
	Administer in cases of asymptomatic vasa previa or placenta previa with a high risk of delivery within 7 days	Low	Strong
	Do not administer prior to transfer unless a diagnosis of preterm labour has been firmly established	Low	Strong
Repeated dose or course	Consider cancellation of a second dose if the risk of preterm delivery decreases significantly following administration of the first dose After cancellation, consider administration of 1 dose or 1 course if a high risk of preterm birth arises, taking into account gestational age and time interval since the first course	Low	Strong
	Do not administer rescue dose or course routinely Gestational age and time interval since the first course of antenatal corticosteroid therapy (at least 14 days) should be taken into account A single rescue course may be administered after risks and benefits are discussed with the woman	Moderate	Conditional

IM: intramuscularly.

**SOGC:
Antenatal
Corticosteroid
Therapy for
Improving
Neonatal
Outcomes
2018**

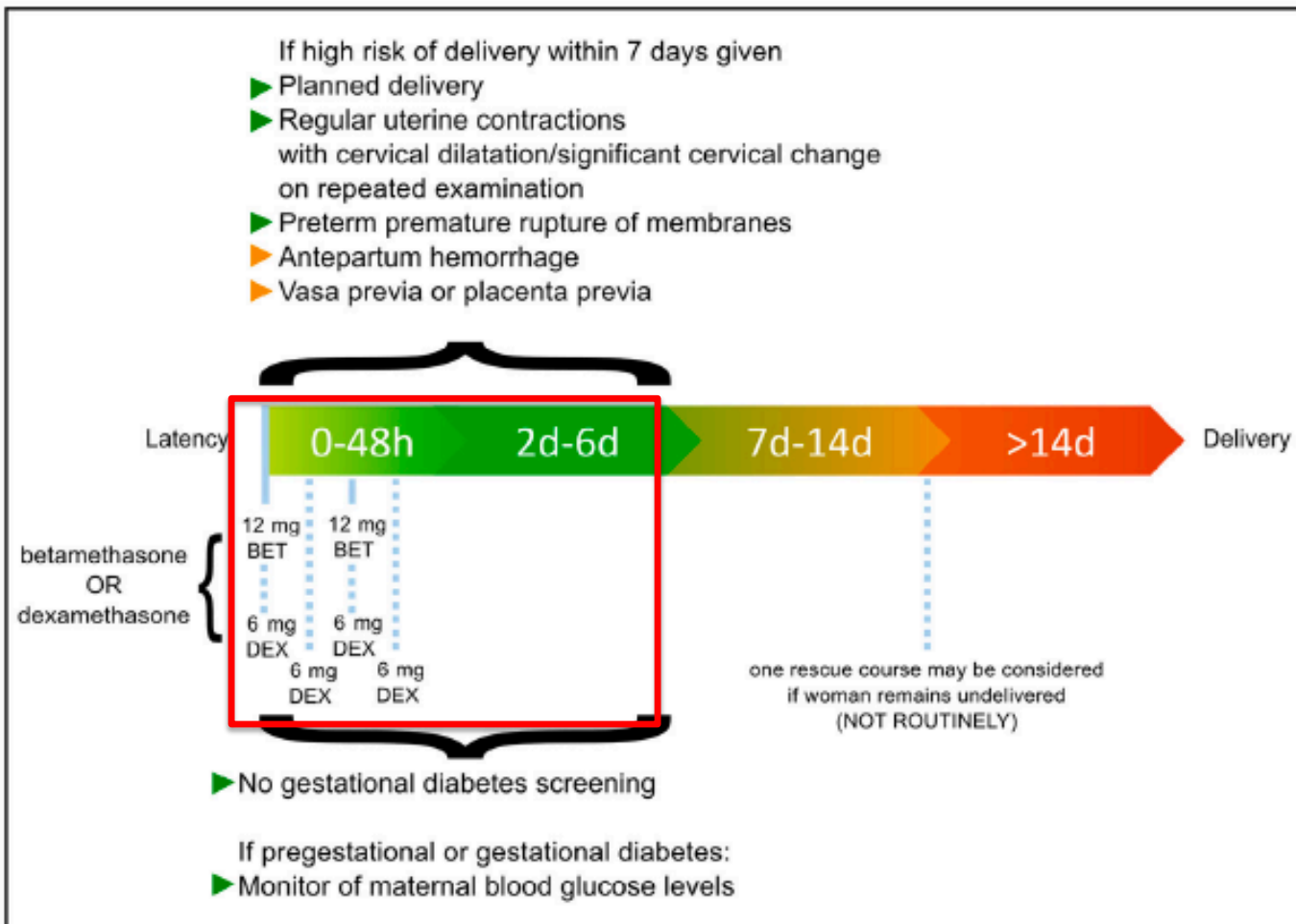
Figure 1. Summary of the evidence.



IVH: intraventricular hemorrhage; Mech Vent: mechanical ventilation; NEC: necrotizing enterocolitis; OR: odds ratio; RR: risk ratio; RDS: respiratory distress syndrome; green arrow: benefit; red arrow: harm. (From S. Mc-

SOGC:
Antenatal
Corticosteroid Use
in Pregnancy
2018

Figure 2. Summary of the evidence (agents, dosage, and target timing). Note: the same recommendation applies to women with multifetal pregnancies, pre-gestational or gestational diabetes, obesity, or growth-restricted fetuses. See the text for further details.

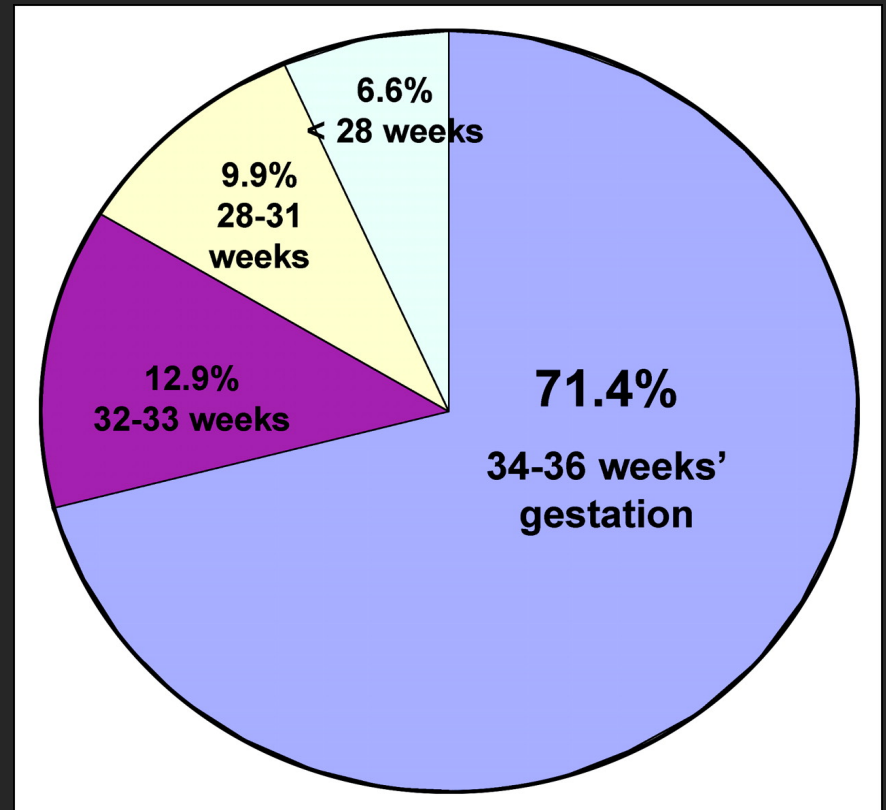


BET: betamethasone: DEX: dexamethasone.

SOGC: Antenatal Corticosteroid Use in Pregnancy 2018

- **Continuous, scheduled doses are not recommended (max 2)**
- **The first dose of the regimen, even if it cannot be completed**
 - **The greatest benefit is 2-7 days after the first dose**

All guidelines agree in the administration of corticosteroids up to gestational age \approx 34 weeks

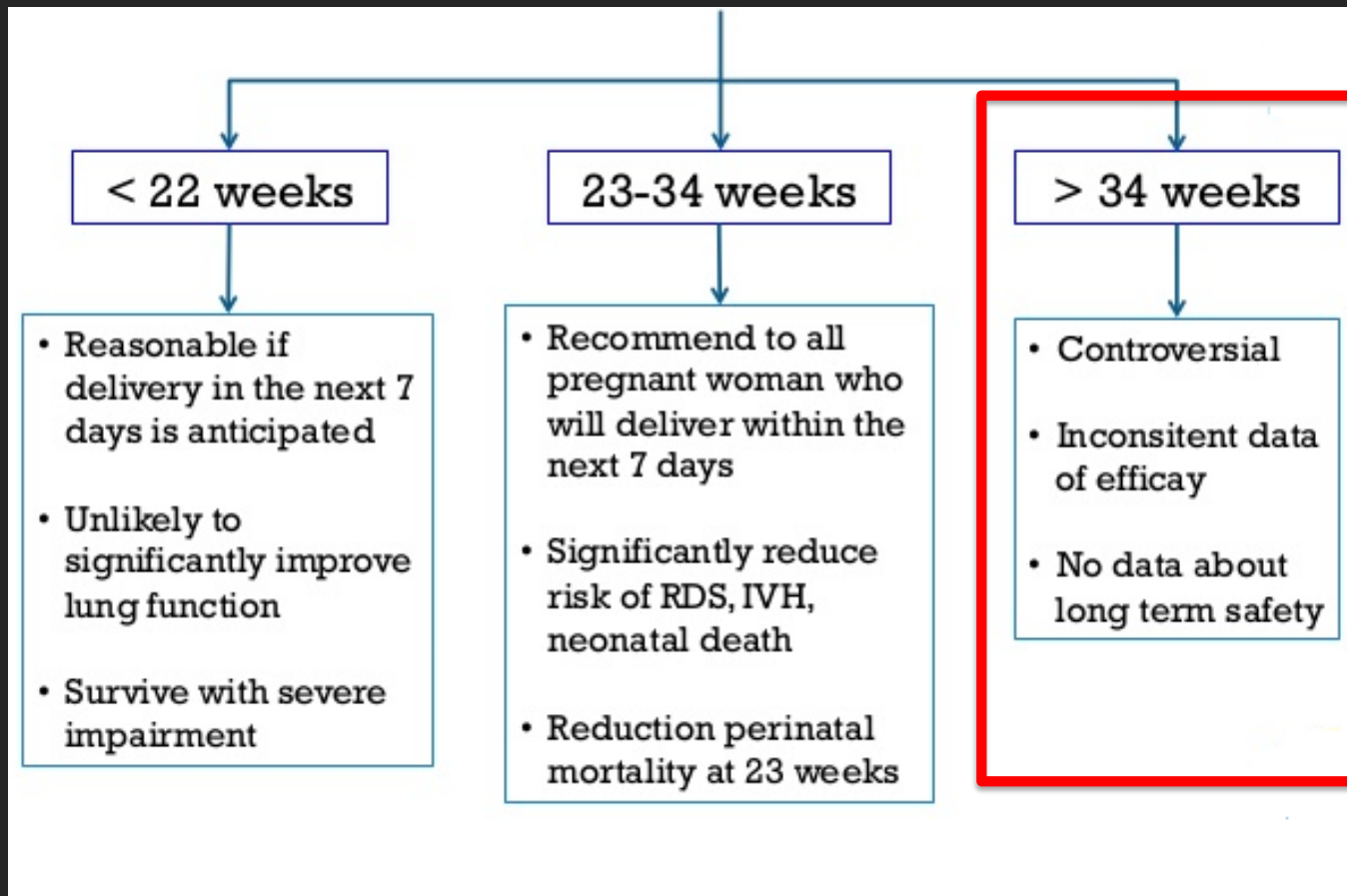


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When to administer corticosteroids?



Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials

Gabriele Saccone,¹ Vincenzo Berghella²

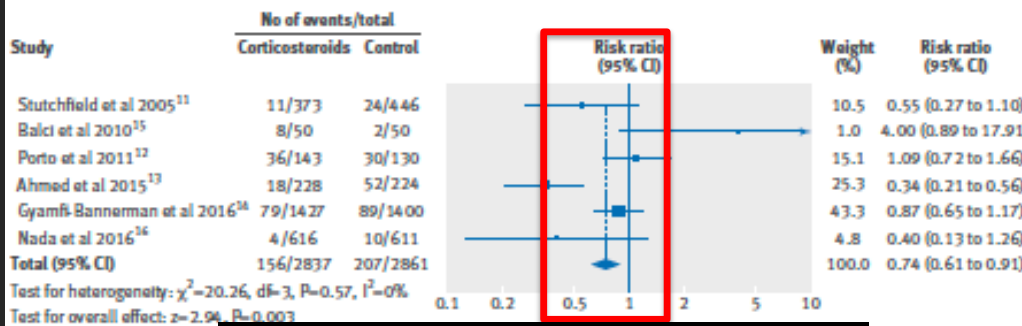


Fig 4 | Forest plot for use Risk of respiratory distress syndrome

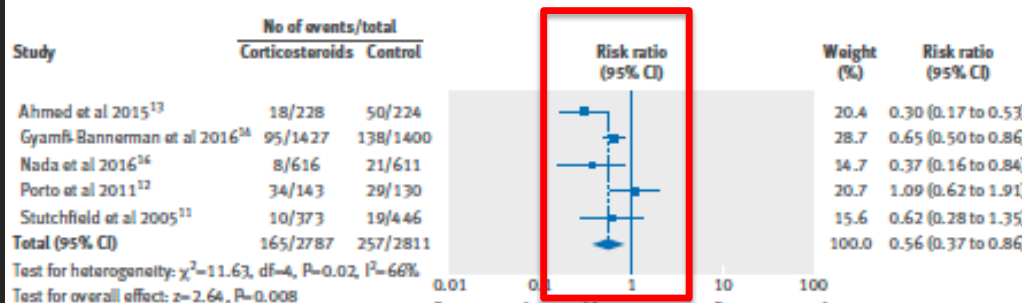


Fig 5 | Forest plot for Risk of transient tachypnea of the newborn

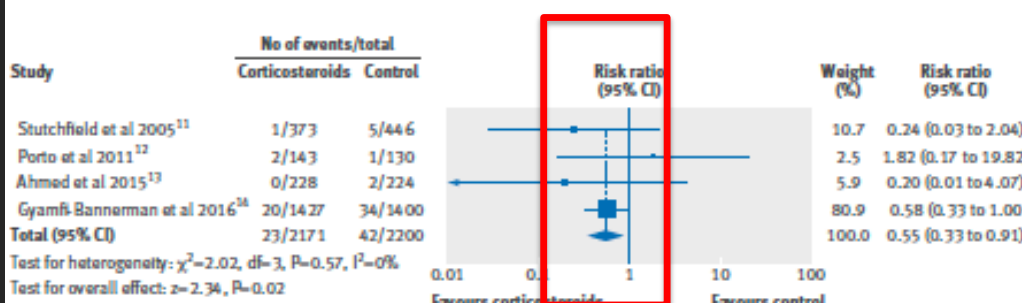


Fig 6 | Forest plot for Risk of severe respiratory distress syndrome

Antenatal steroids at ≥ 34 weeks' gestation reduce neonatal respiratory morbidity

A single course of corticosteroids can be considered for women at risk of imminent late premature delivery 34⁰-36⁶ weeks' gestation, as well as for women undergoing planned cesarean delivery at ≥ 37 weeks' gestation.

Newborn complications by gestational week on delivery by eligibility and reason for ineligibility for antenatal steroids among late preterm deliveries

Gestational week on delivery	34 wk			35 wk			36 wk		
	Eligible N = 315	Ineligible, steroids ^a N = 187	Ineligible, c/d ^b N = 20	Eligible N = 637	Ineligible, steroids ^a N = 149	Ineligible, c/d ^b N = 26	Eligible N = 1411	Ineligible, steroids ^a N = 144	Ineligible, c/d ^b N = 53
	%	%	%	%	%	%	%	%	%
Newborn respiratory complications	24.1	13.9	35.0	14.9	7.4	15.4	5.5	4.9	17.0
Resuscitation at delivery	16.5	11.8	20.0	11.6	8.7	7.7	7.3	6.3	22.6
Glucose instability	7.9	4.8	20.0	5.2	6.0	23.1	3.7	0.7	17.0
NICU admission	87.0	96.3	85.0	45.1	61.7	65.4	20.1	27.8	47.2

NICU, neonatal intensive care unit.

^a Ineligible for late preterm steroids due to prior receipt of antenatal steroids in this pregnancy; ^b Ineligible due to prepregnancy chorioamnionitis or diabetes.

Souter et al. Potential impact of late preterm antenatal steroid guidelines. Am J Obstet Gynecol 2017.

- Careful consideration of which pregnancies should receive late preterm antenatal steroids
- How to identify these pregnancies is important to optimize benefits and mitigate potential risks of this intervention.

Antenatal corticosteroids beyond 34 weeks gestation: What do we do now?

TABLE 2

Studies comparing the use of antenatal corticosteroids for late preterm infants at risk of preterm delivery

Authors	Treatment, n	Control, n	Antenatal corticosteroid used	Deaths, %	Neonatal intensive care admission, %	Respiratory distress syndrome, %	Transient tachypnea of newborn infant, %	Respiratory morbidity, %	Hypoglycemia, %
Balci, et al (2010) ¹⁶	50 Yes	50	Betamethasone: 12 mg × 1 dose 24 hr before delivery	None reported	Only reported as respiratory distress syndrome with admission	4% vs 16% (P=.046)	Did not report	Did not report	Did not report
Porto et al (2011) ¹⁷	143 No	130	Betamethasone: 12 mg × 2 doses, 24 hr apart	0 vs 2 ^a	33 vs 33 ^a	1 vs 1 (P=.54)	24 vs 22 (P=.77)	25 vs 23 (P=.69)	11 vs 7 ^a
Ramadan et al (2016) ¹⁸	74 No	221	Betamethasone: 12 mg × 2 doses, 24 hr apart	0 vs 1 ^a	27 vs 19 (P=.14)	8.1 vs 6.8 (P=.70)	8.1 vs 6.8 (P=.70)	17.6 vs 15.4 (P=.66)	20.3 vs 10.9 (P=.04)
Gyamfi-Bannerman (2016) ¹⁹	1427 Yes	1400	Betamethasone: 12 mg × 2 doses, 24 hr apart	0.1 vs 0 (P=.50)	41.8 vs 44.9 (P=.09)	5.5 vs 6.4 (P=.36)	6.7 vs 9.9 (P<.01)	11.6 vs 14.4 (P=.02) ^b	24.0 vs 15.0 (P<.01)

^a Not significant; no probability value reported. ^b Primary outcome for this study was defined by any of the following occurrences within 72 hours after birth: continuous positive airway pressure or high-flow nasal cannula for at least 2 continuous hours, supplemental oxygen with a fraction of inspired oxygen of ≥ 0.30 for at least 4 continuous hours, mechanical ventilation, stillbirth or neonatal death, or the need for extracorporeal membrane oxygenation.

Kamath-Rayne. Antenatal corticosteroids beyond 34 weeks. *Am J Obstet Gynecol* 2016.

The association of antenatal corticosteroids with neonatal hypoglycemia and hyperbilirubinemia

- Of 6675 preterm deliveries, in neonates exposed to antenatal betamethasone were observed significantly higher rates of:
 - neonatal hypoglycemia (5.7% versus 4.2%, $p < 0.05$)
 - hyperbilirubinemia (45.9% versus 24.1%, $p < 0.05$)
- Controlling for potential confounders including gestational age, these findings persisted with betamethasone-exposed neonates 1.6 times more likely to have hypoglycemia and 3.2 times more likely to have hyperbilirubinemia

Antenatal steroids and neonatal hypoglycemia

- Early preterm (23-33 6/7 wks): 264
- Late preterm (34-36 6/7 wks): 104
- Steroid administration to delivery, (7.9 vs 9.5 days, p.0.12)

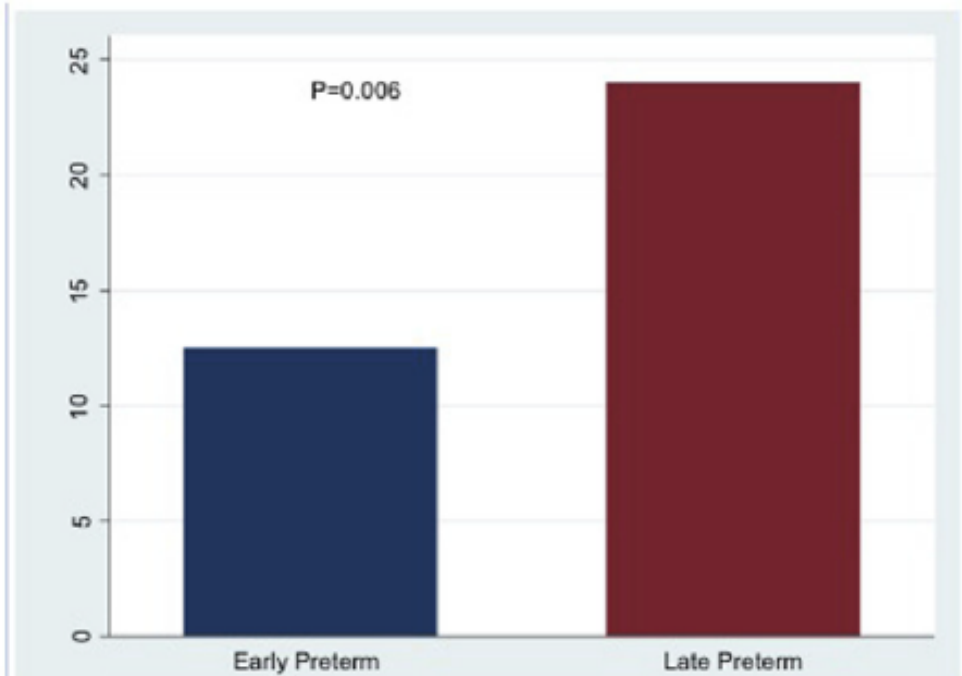
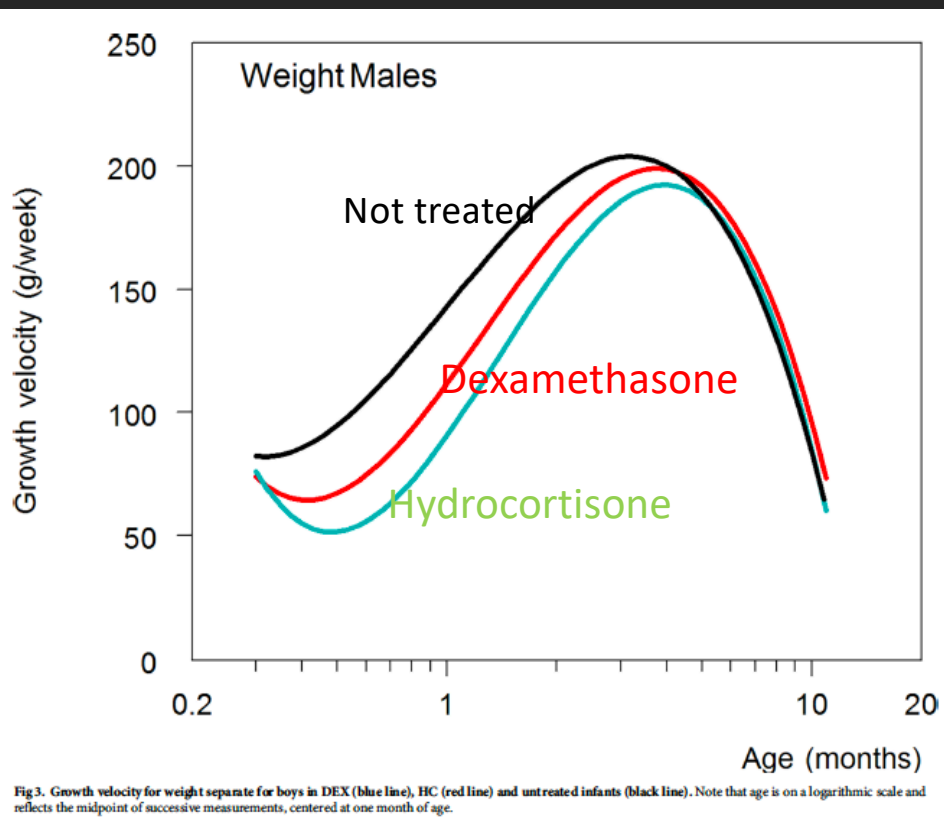


Table: Maternal glucose and neonatal hypoglycemia

Maternal Blood Glucose	Neonatal hypoglycemia	No neonatal hypoglycemia	P
24h after steroids (n=137)			
Mean±SD	145.8 ± 50.8	133.8 ± 40.1	0.19
Median (IQR)	135.5 (123.0, 160.5)	121.0 (111.0, 144.0)	
48h after steroids(n=90)			
Mean±SD	119.9 ± 34.1	124.3 ± 33.0	0.64
Median (IQR)	108.5 (99.0, 134.0)	114.5 (104, 142.0)	
At Delivery (n=100)			
Mean±SD	105.3 ± 36.0	106.9 ± 37.2	0.76
Median (IQR)	100.0 (88.0, 114.0)	103.0 (90.0, 118.0)	

SD=standard deviation; IQR=interquartile range

Neonatal corticosteroid therapy affects growth patterns in early infancy



- Growth velocity curves of corticosteroids treated neonates showed a delay in time
- They had decreased absolute growth velocities during and shortly after treatment and the first two months, followed by an increase in growth velocity in the following months.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

APRIL 7, 2016

VOL. 374 NO. 14

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

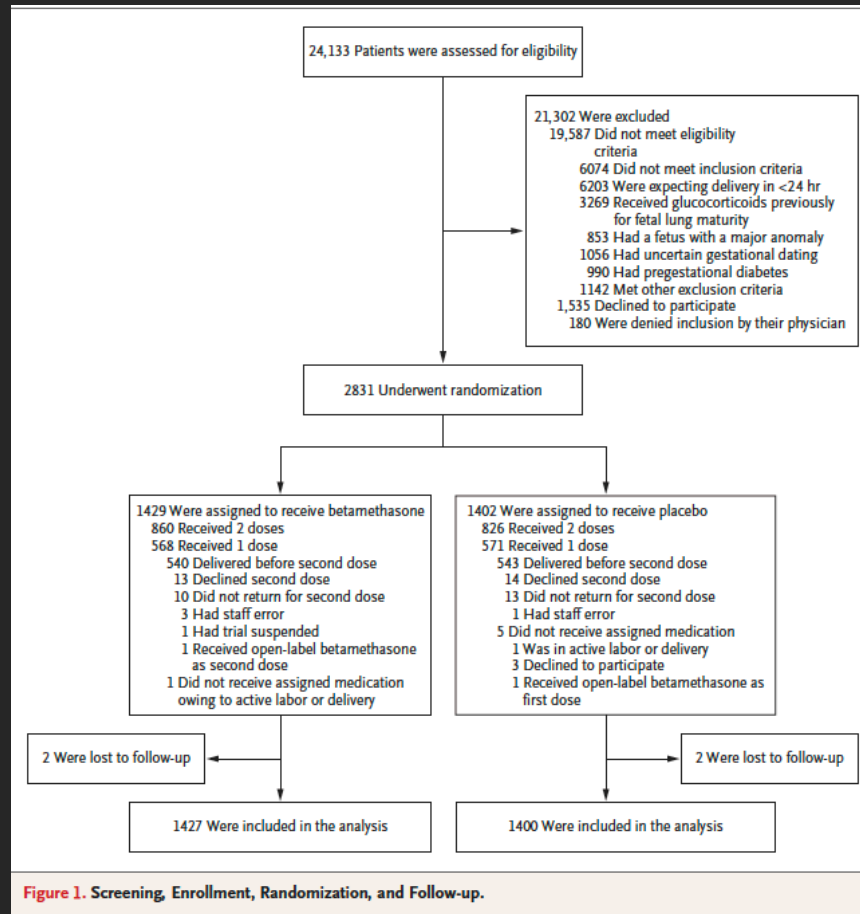


Figure 1. Screening, Enrollment, Randomization, and Follow-up.

Antenatal Betamethasone for Women at Risk
for Late Preterm Delivery

Table 2. Neonatal Respiratory Outcomes.*

Outcome	Betamethasone (N = 1427) no. (%)	Placebo (N = 1400) no. (%)	Relative Risk (95% CI)	P Value
Severe respiratory complications†	115 (8.1)	160 (12.1)	0.67 (0.53–0.84)	<0.001
Hypoglycemia — no. (%)†	343 (24.0)	210 (15.0)	1.60 (1.37–1.87)	<0.001
Need for resuscitation at birth§	206 (14.5)	260 (18.7)	0.78 (0.66–0.92)	0.003
Transient tachypnea of the newborn	95 (6.7)	138 (9.9)	0.68 (0.53–0.87)	0.002
Apnea	33 (2.3)	37 (2.6)	0.88 (0.55–1.39)	0.57
Mechanical ventilation	34 (2.4)	43 (3.1)	0.78 (0.50–1.21)	0.26
Respiratory distress syndrome	79 (5.5)	89 (6.4)	0.87 (0.65–1.17)	0.36

Summary of studies regarding antenatal corticosteroid therapy between 34⁺⁰ - 36⁺⁶ weeks of gestation

Studies		No. of patients		Effect		Certainty	Importance
No. of studies	Study design	ACS	No treatment (or placebo)	RR (95% CI)	Absolute (95% CI)		
Perinatal death							
3	RCT	6/1658 (0.4%)	6/1638 (0.4%)	RR 1.03 (0.29–3.67)	0 fewer per 1000 (from 3 fewer to 10 more)	⊕○○○ Very low	Critical
Respiratory distress syndrome							
6	RCT	102/1901 (5.4%)	202/1882 (10.7%)	RR 0.71 (0.56–0.91)	31 fewer per 1000 (from 10 fewer to 47 fewer)	⊕⊕⊕○ Moderate	Important
Chorioamnionitis							
3	RCT	20/1604 (1.2%)	35/1598 (2.2%)	RR 0.57 (0.33–0.99)	9 fewer per 1000 (from 0 fewer to 15 fewer)	⊕⊕○○ Low	Important
Hypoglycemia							
3	RCT	367/1666 (22.0%)	222/1628 (13.6%)	RR 1.62 (1.39–1.88)	85 more per 1000 (from 53 more to 120 more)	⊕⊕⊕○ Moderate	Important

RCT: randomized controlled trial.

Based on data from Roberts et al.²⁷ and additional information from original studies.

- The balance of benefits and risks supports routine antenatal corticosteroid at $34^{+0} - 34^{+6}$ weeks
- Does not support routine antenatal corticosteroid therapy at $35^{+0} - 35^{+6}$ and especially at $36^{+0} - 36^{+6}$ weeks

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Survival & Major morbidity in extremely premature infants

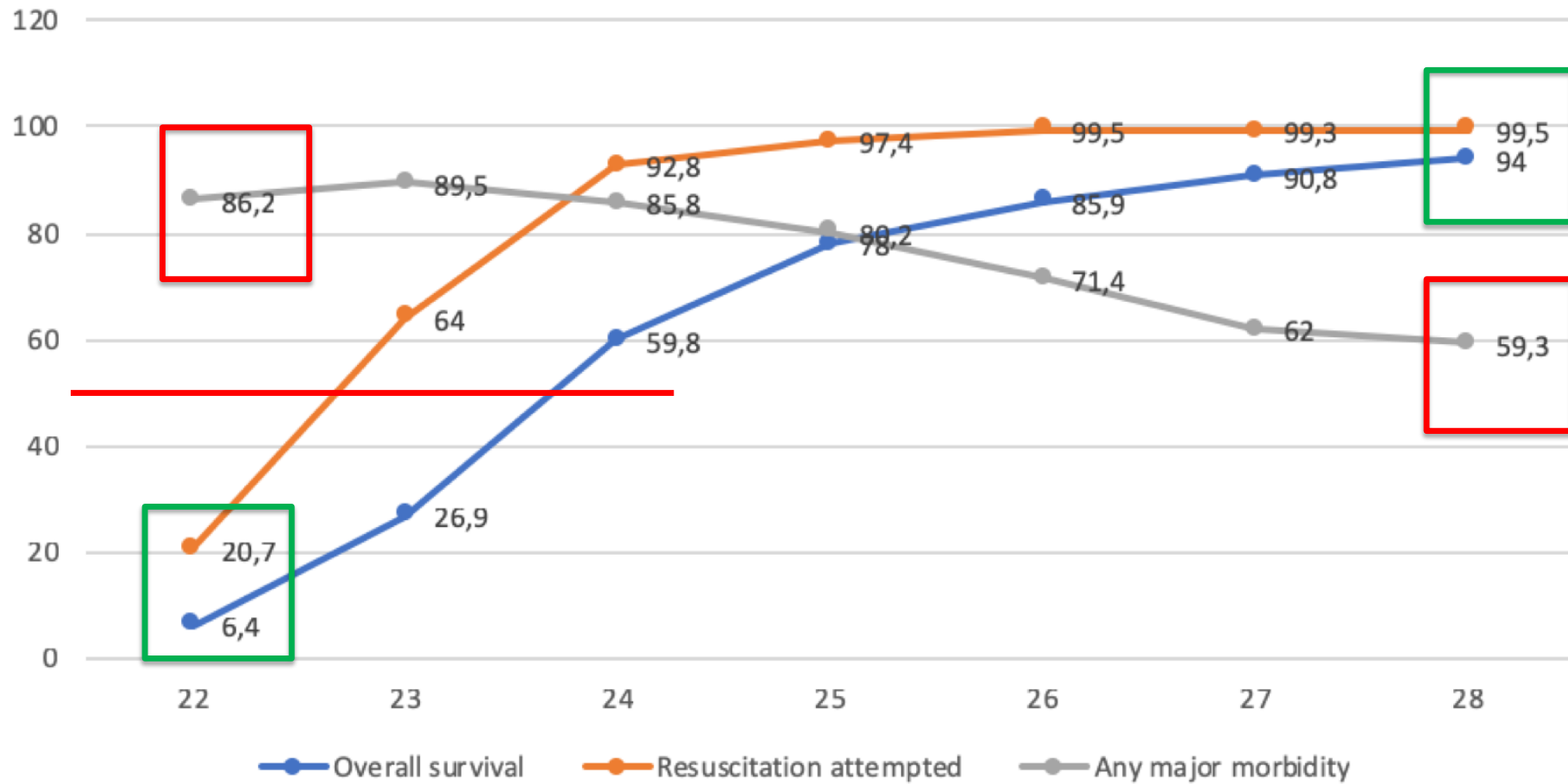
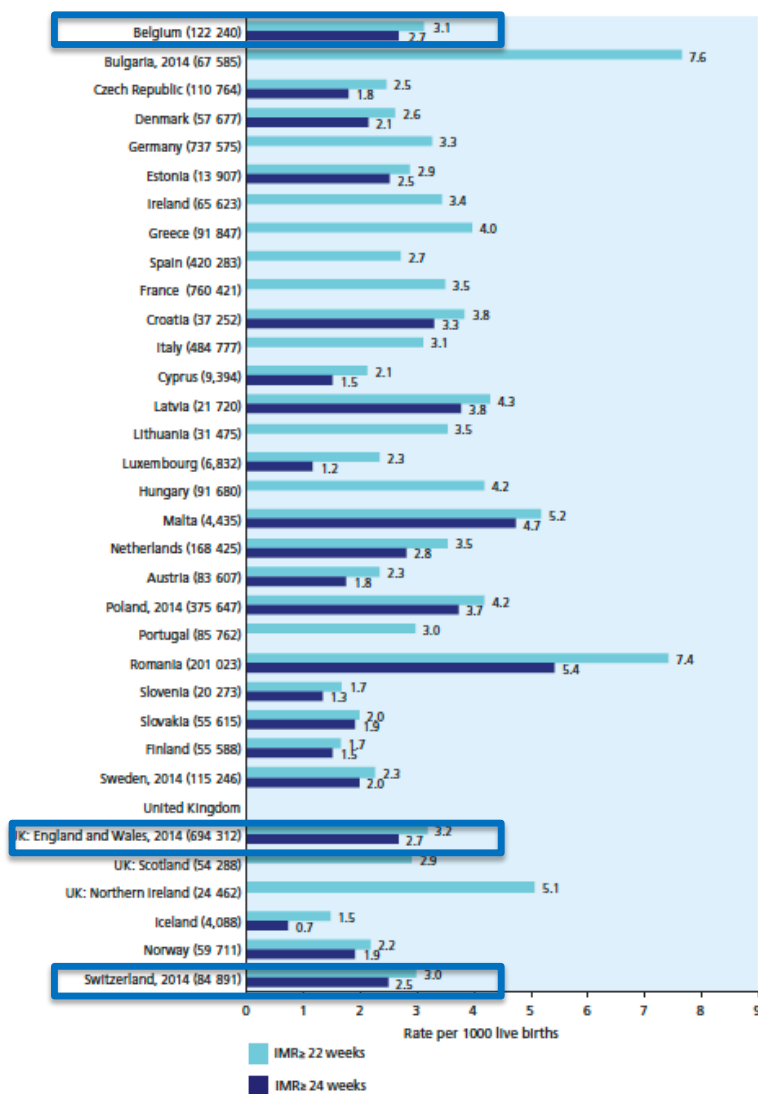
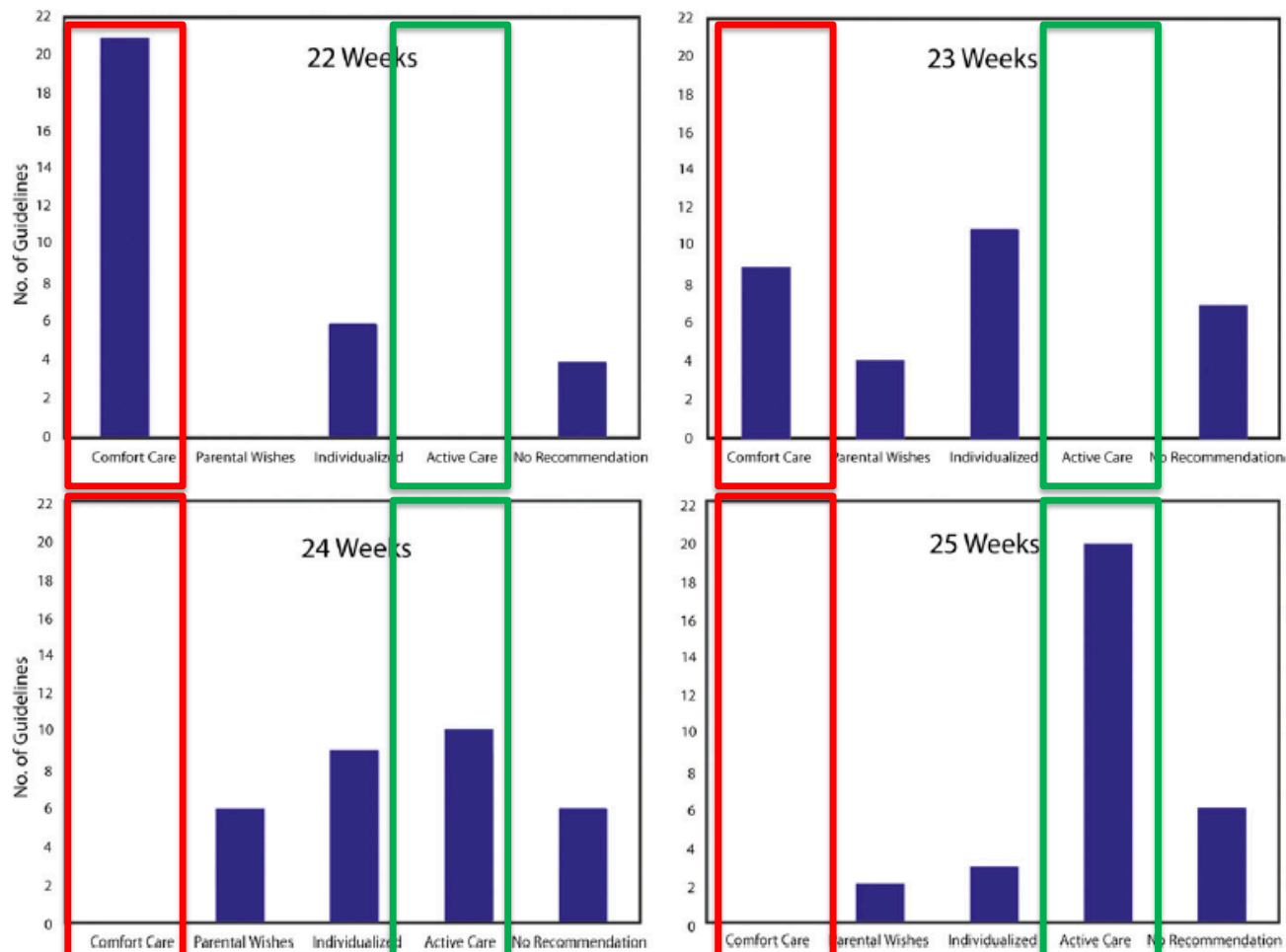


Figure C3.2 Infant mortality at and after 22 and 24 weeks in 2015



NOTE: Data are cohort data when available (Belgium, Denmark, Estonia, Croatia, Cyprus, Latvia, Malta, Austria, Slovenia, Finland, Northern Ireland, Iceland, Norway, England and Wales, and Switzerland) or annual rates when cohort data were not available (Bulgaria, Czech Republic, Germany, Ireland, Greece, Spain, France, Italy, Lithuania, Luxembourg, Hungary, Netherlands, Poland, Portugal, Romania, Scotland, Slovakia, and Sweden).

Guidelines for neonatal care in extreme preterm deliveries of different countries



AC	Active Care
CC	Comfort Care
IND	Individualized Care
NR	No Recommendation
PW	Parental Wishes

Ú. Guillén, et al: Pediatrics, 2015

NICHD Extremely Preterm Birth Outcome Data

Enter the characteristics below.

Gestational Age (*Best Obstetric Estimate in Completed Weeks*):

Birth Weight (*401 Grams to 1,000 Grams*): grams

Sex: Female Male

Singleton Birth: Yes No

Antenatal Corticosteroids (*Within Seven Days Before Delivery*): Yes No

[View Outcome Estimates](#)

[Clear](#)

[Back to main page](#)

Based on the following characteristics:

Gestational Age (*Best Obstetric Estimate in Completed Weeks*): 22 weeks
 Birth Weight: 550 grams
 Sex: Female
 Singleton Birth: Yes
 Antenatal Corticosteroids: Yes

Estimated outcomes* for infants in the NRN sample are as follows:

Outcomes	Outcomes for All Infants	Outcomes for Mechanically Ventilated Infants
Survival	11%	30%
Survival Without Profound Neurodevelopmental Impairment	6%	18%
Survival Without Moderate to Severe Neurodevelopmental Impairment	3%	11%
Death	89%	70%
Death or Profound Neurodevelopmental Impairment	94%	82%
Death or Moderate to Severe Neurodevelopmental Impairment	97%	89%

TABLE 3**General guidance regarding obstetric interventions for threatened and imminent periviable birth by best estimate of gestational age^a**

	20 0/7 weeks to 21 6/7 weeks	22 0/7 weeks to 22 6/7 weeks	23 0/7 weeks to 23 6/7 weeks	24 0/7 weeks to 24 6/7 weeks	25 0/7 weeks to 25 6/7 weeks
Neonatal assessment for resuscitation ^a	Not recommended 1A	Consider 2B	Consider 2B	Recommended 1B	Recommended 1B
Antenatal corticosteroids	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Tocolysis for preterm labor to allow for antenatal corticosteroid administration	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Magnesium sulfate for neuroprotection	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Antibiotics to prolong latency during expectant management of preterm PROM if delivery is not considered imminent	Consider 2C	Consider 2C	Consider 2B	Recommended 1B	Recommended 1B
Intrapartum antibiotics for group B streptococci prophylaxis ^b	Not recommended 1A	Not recommended 1A	Consider 2B	Recommended 1B	Recommended 1B
Cesarean delivery for fetal indication ^c	Not recommended 1A	Not recommended 1A	Consider 2B	Consider 1B	Recommended 1B

PROM, premature rupture of membranes.

^a Survival of infants born in the periviable period is dependent on resuscitation and support. Between 22 weeks and 25 weeks of gestation, there may be factors in addition to gestational age that will affect the potential for survival and the determination of viability. Importantly, some families, concordant with their values and preferences, may choose to forgo such resuscitation and support. Many of the other decisions on this table will be linked to decisions regarding resuscitation and support and should be considered in that context; ^b Group B streptococci carrier, or carrier status unknown;

^c For example, persistently abnormal fetal heart rate patterns or biophysical testing, malpresentation.

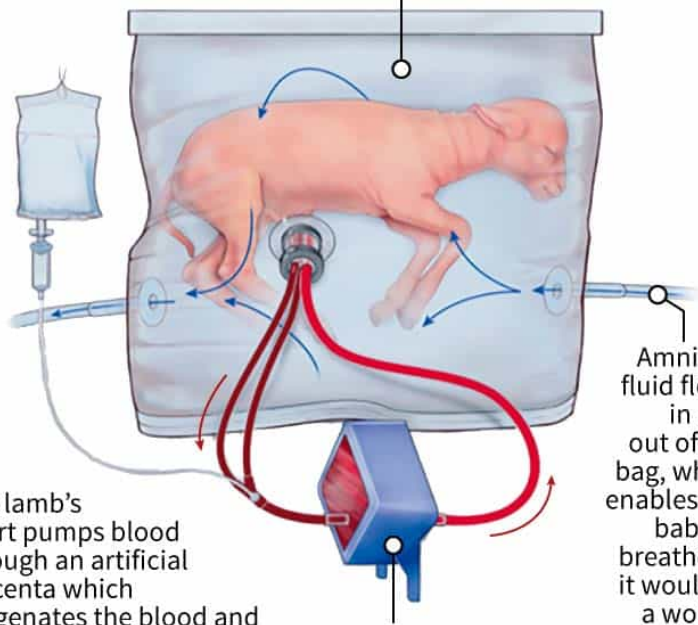
ACOG. *Periviable birth*. *Am J Obstet Gynecol* 2016.

Artificial womb

How the artificial womb works

This device, currently tested on lambs which have similar prenatal lung development to humans, could transform care for extremely premature babies.

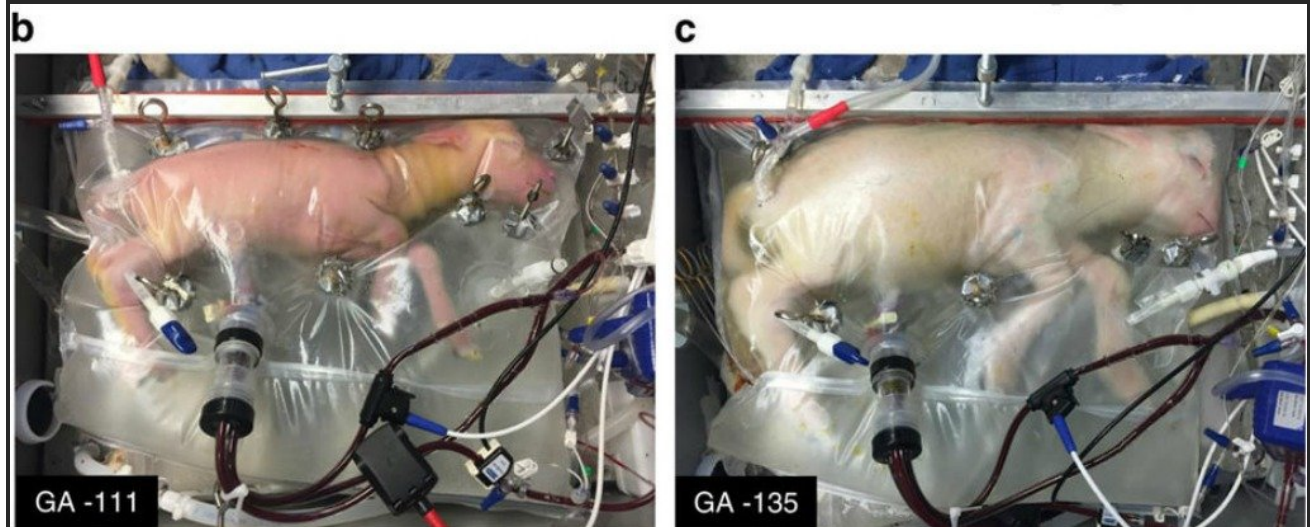
The premature lamb is placed into a temperature-controlled biobag.



The lamb's heart pumps blood through an artificial placenta which oxygenates the blood and adds heparin (blood thinner).

Amniotic fluid flows in and out of the bag, which enables the baby to breathe as it would in a womb.

SOURCE/ILLUSTRATION: CHILDREN'S HOSPITAL OF PHILADELPHIA



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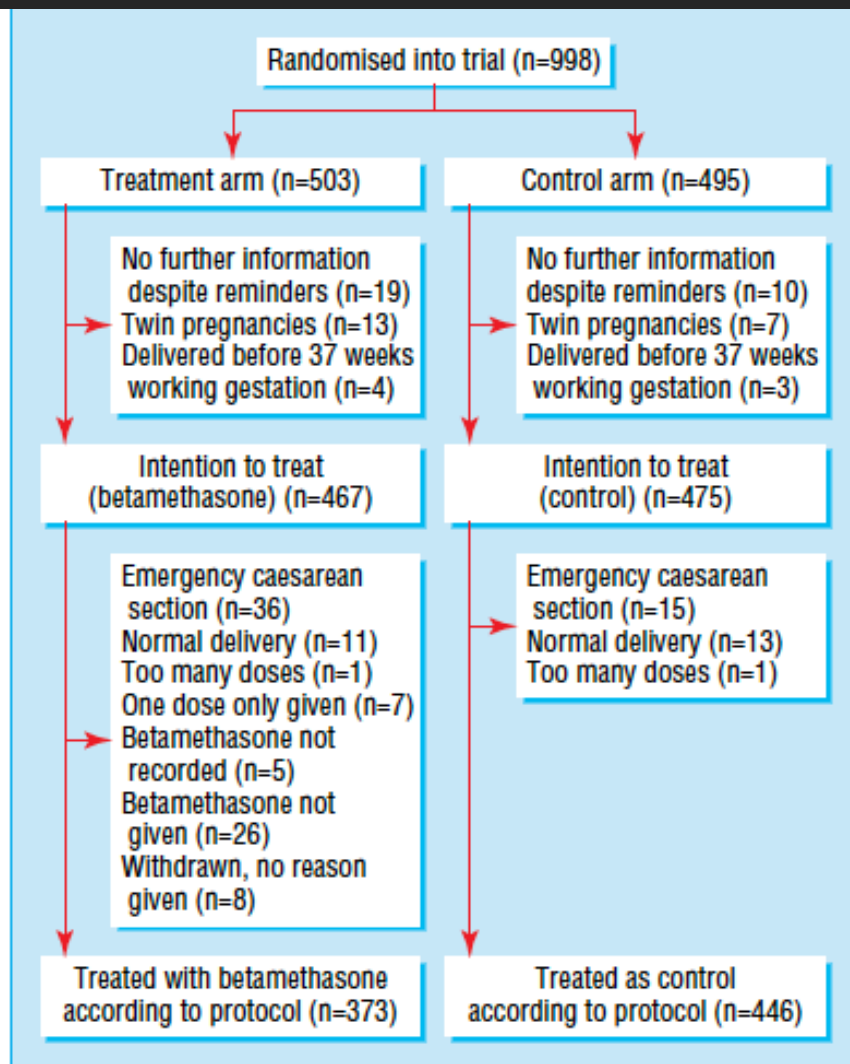


Fig 1 Flow of participants through the trial

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

BMJ, 2005

Risk of respiratory morbidity in term infants delivered by elective caesarean section

Gestational age† and type of delivery	No of deliveries	No (%) of infants	No (%) of infants
37 weeks:			
Elective caesarean section	261	26 (10.0)	5 (1.9)
38 weeks:			
Elective caesarean section	1173	60 (5.1)	10 (0.9)
39 weeks:			
Elective caesarean section	1074	23 (2.1)	2 (0.2)
40 weeks:			
Elective caesarean section	132	2 (1.5)	0 (0.0)
Intended vaginal delivery	11 177	180 (1.6)	16 (0.1)
(Reference)			

Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial)

Peter Roy Stutchfield,¹ Rhiannon Whitaker,² Angela E Gliddon,² Lucie Hobson,³ Sailesh Kotecha,⁴ Iolo J M Doull⁵

Table 2 Summary of scores for the strengths and difficulties subscales for the participants by treatment group and school assessment of additional help and quartile of ability

	Control	Betamethasone		
Prosocial scale	8.58 (1.66)	8.72 (1.76)	0.14 (-0.19 to 0.48)	0.90
Additional help required n (%)	N=166 22 (13.3)	N=189 34 (18.0)	$\chi^2(1)=1.492$	0.22
School assessment of child's quartile of ability	N=164	N=186		
Top quarter of academic ability	74 (45.1)	70 (37.6)	$\chi^2(2)=6.74$	0.03
Middle half of academic ability	76 (46.3)	83 (44.6)		
Lower quarter of academic ability	14 (8.5)	33 (17.7%)		

Antenatal betamethasone

- did not result in any adverse outcomes or reduction in asthma or atopy
 - had lower academic ability
- It should be considered for elective CS at 37–38 weeks of gestation

Administration of corticosteroids in late preterms. The controversy.

- **History and instructions for administration**
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- **Comparison of guidelines**



Prelabor Rupture of membranes

>37 ⁺⁰	34 ⁺⁰ -36 ⁺⁶	24 ⁺⁰ -33 ⁺⁶	<23 ⁺⁶
Deliver (induced with OXT (12-18h) (prostaglandins equally effective, but more chorioamnionitis)	Recommend Delivery (<i>option of expectant management until 37wks -discuss risks/benefits</i>)	Expectant management if no maternal/fetal contraindication	counselling
Corticosteroids NO	Corticosteroids <i>ONLY if they were NOT given till then</i>	Corticosteroids YES	Expectant/induction
	Treat intraamniotic infection if present	Antibiotics (for latency)	Antibiotics YES >20wks
~ GBS prophylaxis YES	~ GBS prophylaxis YES	~ GBS prophylaxis YES MgSO4 if birth anticipated <32wks (cerebral palsy)	GBS prophylaxis No <23+6 MAYBE >24 ⁺⁰ ,

SOGC: Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes 2018

Table 8. Summary table of recommendations according to subpopulation

Subpopulation	Recommendation given high risk of delivery within 7 days and if gestational age criteria are met	Level of evidence	Strength of recommendation
Multifetal gestation	Administer according to the same indications and in the same gestational age range as for singleton pregnancies		
Pre-gestational or gestational diabetes	Administer at the same dosage, according to the same indications and in the same gestational age range as that recommended for non-diabetic women Pay close attention to control of maternal blood glucose in the days following	Low	Conditional
	Administer at the same dosage, according to the same indications and in the same gestational age range as that recommended for non-diabetic women	Low	Strong
Obesity	Administer at the same dosage as that recommended for women without obesity	Low	Conditional
Intrauterine growth restriction	Administer according to the same indications and in the same gestational age range as in normal pregnancies after risks and benefits are discussed with the woman diagnosis unless there is a high risk of preterm birth within the next 7 days		

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Repeated antenatal corticosteroids: effects on cerebral palsy and childhood behavior

- Nonrandomized regional cohort of 541 very preterm infants born in Western Australia from singleton pregnancies and alive at 3 & 6 years
- Increasing numbers of antenatal corticosteroid courses were associated with a reduction in the rate of cerebral palsy
- **Three or more courses** were also associated with **increased rates of aggressive/destructive, distractible, and hyperkinetic behavior** and these effects were present at both ages 3 and 6 years



Cesarean Section, corticosteroids and neurodevelopment

Multiple doses of corticosteroids

Laboratory animals

Low birth weight
Reduced brain weight
Reduced number of neurons
Delayed myelination

Ikegami 1997, Moss 2006, Huang 1999, Uno 1990, Huang 2001, Sloboda 2002

Human

Reduced head circumference

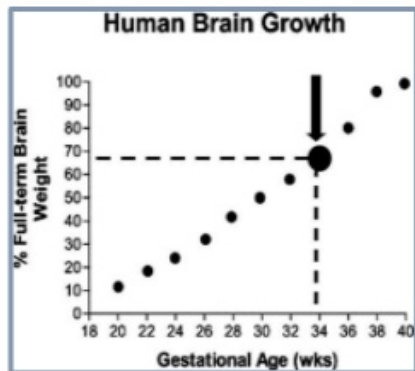
French 1999, Kumar 2005

Outcome	Term (≥ 37 weeks) N = 462	
	Multiple ACS N = 213 ^a	Single ACS N = 249
Death or severe disability (neuromotor, neurosensory, neurocognitive) [§]	48/213 (22.5%)	38/249 (15.3%)
Death up to 5 years	1/213 (0.5%)	2/249 (0.8%)
Neuromotor disability ^{††} (non-ambulatory cerebral palsy)	0/212 (0%)	1/247 (0.4%)
Neurosensory disability	19/212 (9.0%)	7/247 (2.8%)
Needing visual aids	17/212 (8.0%)	7/247 (2.8%)
Deafness	3/212 (1.4%)	1/247 (0.4%)
Pre-existing (diagnosed at 2 years or earlier)	0	0
New (diagnosed after 2 years of age)	3	1
Neurocognitive/neurobehavioural disability	31/212 (14.6%)	30/246 (12.2%)

Outcomes of children at 5 years by gestational age at birth and ACS groupings

Fetal brain

Fetal Brain Growth at 34 Weeks Gestation is 65% of Full-Term Weight



- Brain weight at different ages from 20 to 40 gestational weeks is illustrated at each gestational age as a percent of term brain weight.
- At 34 gestational weeks, the overall brain weight is 65% of term weight. Arrow highlights brain weight at 34 weeks' gestation.

The percent brain weights were based on the data of Guillard-Costa and Larroche (1990).

(Jain, 2008; Kinney, 2006 in 2008)

Brain tissue are uniquely vulnerable during moderate and late Preterm Birth

Cortical Gray Matter weight increases approximately 50%.

Major Brain Development occurs during the Moderate (32-33 weeks) and Late Preterm (34-36 weeks) Periods of Gestation

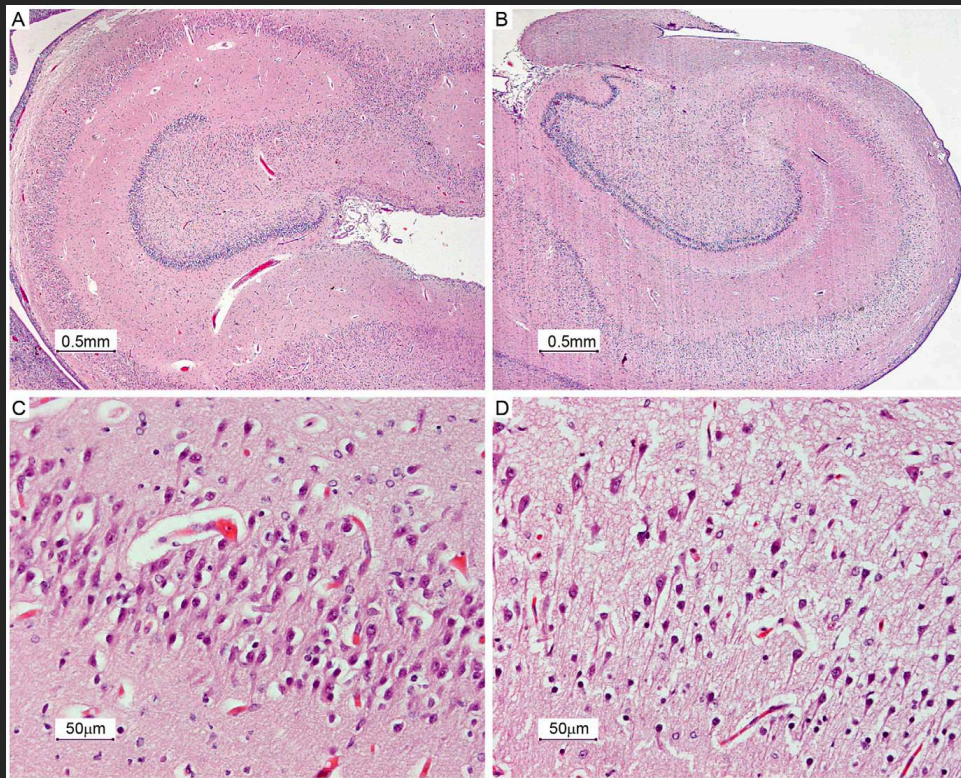
Myelinated White Matter Volumes increase by 5-Fold

Cerebellar Volume Increase by 25%

(Cheong, et al., 2016; Huppi, et al., 1998 in 2016; Limperopoulos, et al., 2005 in 2016; Sciencemag.org, 2015)

ozella.brundidge@gmail.com 4/9/2017

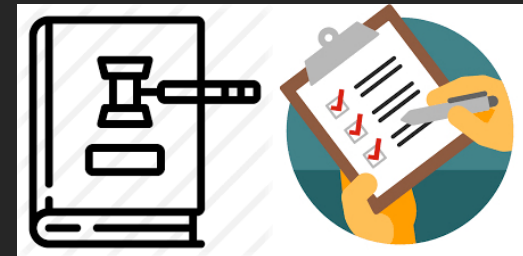
Effects of Antenatal Glucocorticoid Therapy on Hippocampal Histology of Preterm Infants



- The hippocampi of ten neonates who had been treated with antenatal glucocorticoids showed **a lower density of large neurons** ($p = 0.01$) and
- **Neurons irrespective of size** ($p = 0.02$) as compared to eleven neonates who had not been treated with glucocorticoids

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Comparison of guidelines for administration of corticosteroids in pregnancy

	NICE Clinical Guideline	ACOG Committee Opinion	SOGC Guideline	New Zealand and Australian Guidelines	WHO recommendations	FIGO Committee report
Country	United Kingdom	United States	Canada	New Zealand and Australia	International	International
Issued	2019	2017	2018	2015	2015	2019
Corticosteroid regimens	Not mentioned	IM dexamethasone or betamethasone	IM dexamethasone or betamethasone	IM dexamethasone or betamethasone	IM dexamethasone or betamethasone	IM dexamethasone or betamethasone
Timing	24 ⁺⁰ - 33 ⁺⁶	24 ⁺⁰ - 34 ⁺⁰	24 ⁺⁰ - 34 ⁺⁶	24 ⁺⁰ - 34 ⁺⁶	24 ⁺⁰ - 34 ⁺⁰	24 ⁺⁰ - 34 ⁺⁰
Perivable period	23 ⁺⁰ -23 ⁺⁶ discuss with the woman	23 ⁺⁰ and 23 ⁺⁶ may be considered. Perivable period should be considered	22 ⁺⁰ -23 ⁺⁶ should be considered	Not mentioned	Not mentioned	linked to family's decision regarding resuscitation. Based on local limits of viability
Late preterm period	34 ⁺⁰ and 35 ⁺⁶	34 ⁺⁰ -36 ⁺⁶	35 ⁺⁰ -36 ⁺⁶			34 ⁺⁰ -36 ⁺⁶
	Consider	Recommended if no previous course	Maybe after risks and benefits are discussed	Not mentioned	Not mentioned	Recommended if no previous course

Comparison of guidelines for administration of corticosteroids in pregnancy

	NICE Clinical Guideline	ACOG Committee Opinion	SOGC Guideline	New Zealand and Australian Guidelines	WHO recommendations	FIGO Committee report
Country	United Kingdom	United States	Canada	New Zealand and Australia	International	International
Issued	2019	2017	2018	2015	2015	2019
Repeated doses and rescue course of corticosteroids	No repeat courses of corticosteroids. Take into account the interval from the last course, gestational age and the likelihood of birth within 48 hours	No repeat courses of corticosteroids. Should be considered if prior course more than 14 days before. Rescue course could be provided as early as 7 days from the prior dose	No repeat courses of corticosteroids. Rescue course should be considered after a time interval of at least 14 days	A single repeat course of corticosteroids, if preterm labor does not occur within 7 days is recommended or up to 3 single repeat doses before 32+6w	A single repeat course of antenatal corticosteroids if preterm labor does not occur within 7 days after the initial dose is recommended	No repeat courses of corticosteroids, (more than two). Refers to ACOG and WHO
CS	Not mentioned	Not mentioned	Not recommended at term	48 h prior to planned CS > 34+6w, only if known fetal lung immaturity.	Not recommended in late preterm	Consider for planned CS at 37–38+6 w.

Use of corticosteroids in pregnancy

- YES
 - 24-34⁺⁰ weeks
 - 24-34⁺⁶ weeks
- CONSIDER (if no previous course was given)
 - 34-36⁺⁶ weeks
 - 35-36⁺⁶ weeks
- CONSIDER repeat doses
 - If prior course >14 days
 - No more than 2

Use of corticosteroids in pregnancy

- Rescue dose: Consider
 - If prior course >14 days
- pPROM:
 - <34 weeks: YES
 - >34 weeks: Only if they were not given till then
- Elective CS: Delay elective CS till 39⁺⁰
 - 37-38 weeks: Consider
 - 39 weeks: NO.

Table 4. Summary table of recommendations according to gestational age

Gestational age	Recommendation in case of high risk of delivery within 7 days	Level of evidence	Strength of recommendation
<24 + 0 weeks	Administration based on desire for early intensive care by woman in consultation with health care providers	Low	Conditional
24 + 0 to 34 + 6 weeks	Routine administration	Moderate	Strong
35 + 0 to 35 + 6 weeks	Administration based on discussion of risk and benefits with patients	Moderate	Conditional
36 + 0 to 36 + 6 weeks	Administration restricted to specific clinical situations	Moderate	Conditional
Elective Caesarean delivery at term	Not recommended	Low	Strong

- Antenatal corticosteroids can continue to be used in women at high risk of preterm birth. Further information is required regarding the optimal dose-to-delivery interval, the optimal steroid, the effects in multiple pregnancy and long-term effects into adulthood. We advise that birth should not be delayed to administer antenatal corticosteroids when there are serious concerns about maternal condition that will be alleviated by expedited delivery.

Subgroup analysis and investigation of heterogeneity

We performed analysis of clinical groups for primary outcomes only (where data were available).

We analysed the following clinical groups:

1. singleton versus multiple pregnancy;
2. intact membranes versus ruptured membranes at first dose;
3. pregnancy-induced hypertension syndromes;
4. type of glucocorticoid (betamethasone, dexamethasone, hydrocortisone);
5. decade of trial (post-hoc, i.e. not pre-specified in the protocol);
6. protocol with weekly repeats (post hoc, i.e. not pre-specified in the protocol);
7. gestational age at trial entry (post hoc, i.e. not pre-specified in the protocol).

Χρήση κορτικοστεροειδών στην κύηση ACOG 2017

Late preterm period
34-37 α (+ PEY)

Preterm period
24-34wks (+ PEY)

Previability period
23-24 wks (+ PEY)

Ναι
αν δεν έχει
δοθεί
έως τότε

Όχι
αν κλινική
χοριοαμνιονιτιδα
ή σοβαρή
προεκλαμψία ή
επείγουσα
κατάσταση

τοκετός

Ναι

Επανάληψη σχήματος?

**Αν δεν είναι
PEY**
↓
Ναι

Αν είναι PEY
**Insufficient
data**

**Αν προηγούμενο σχήμα
>7-14 μέρες πριν**

May be considered
(αν επίκειται
τοκετός στις
επόμενες 7 ημέρες)