Antenatal / Postnatal steroids and outcomes following preterm birth

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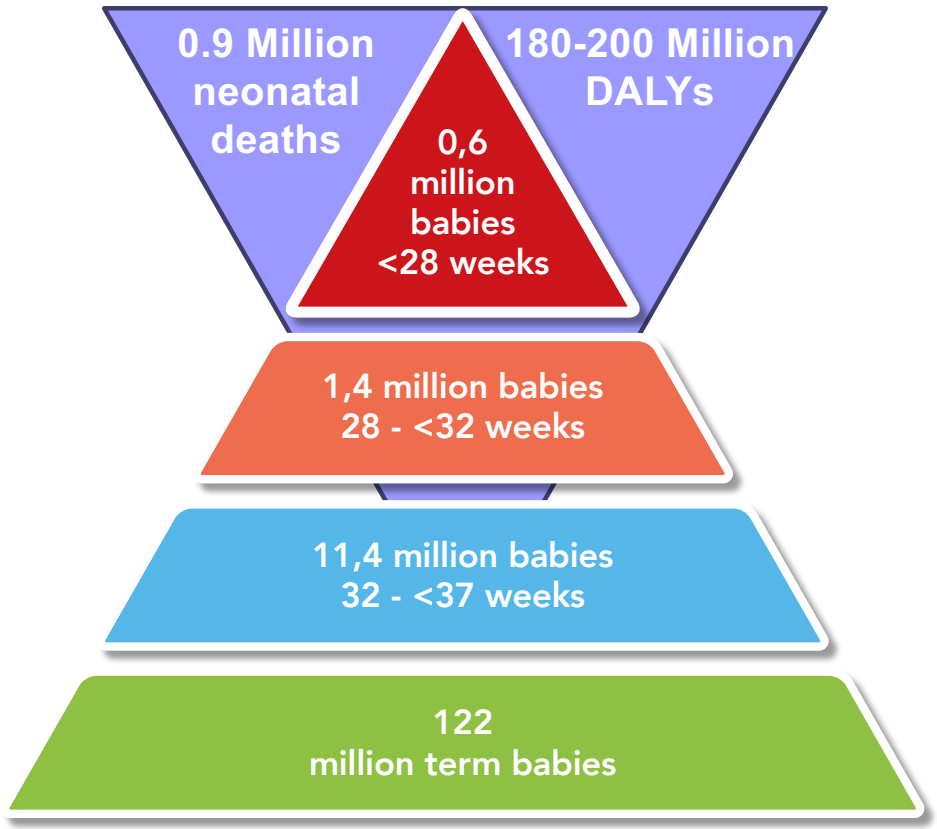
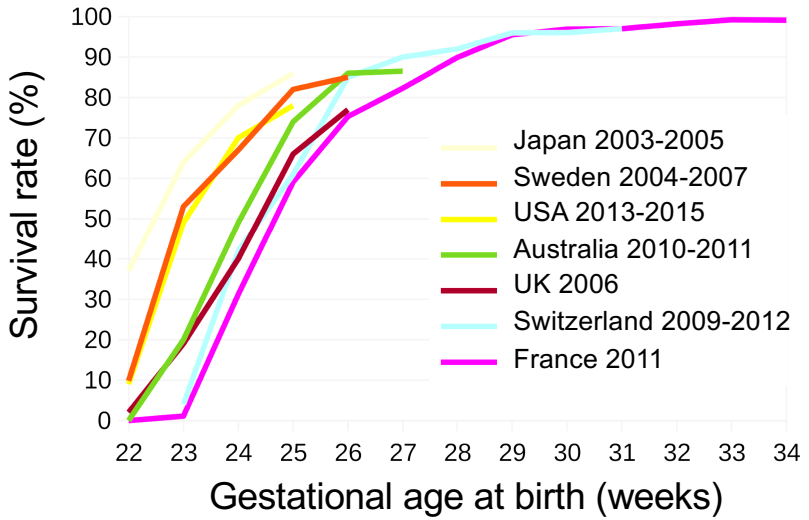
Groupement Belge de Néonatologie, Novembre 2024

Prematurity and neonatal mortality





Lawn JE, et al. Lancet 2023
Ancel PY et al., JAMA Ped 2015
Trinh NTH et al., Lancet Reg Health Eur 2022

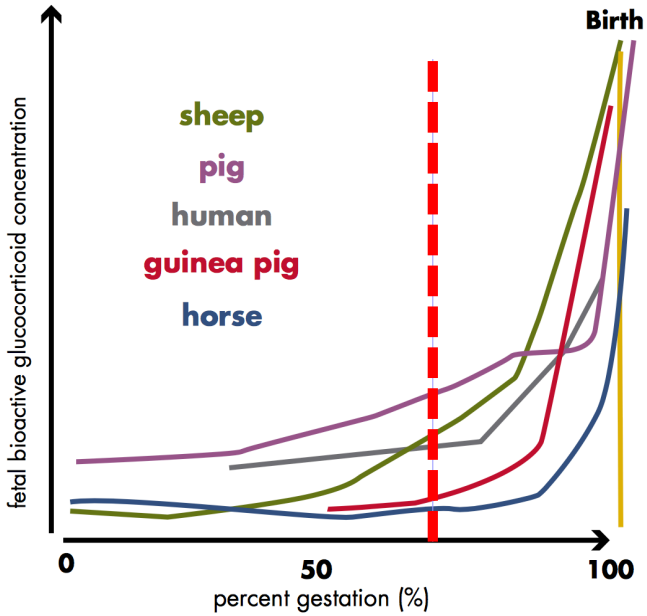
Prematurity and neonatal mortality: main causes

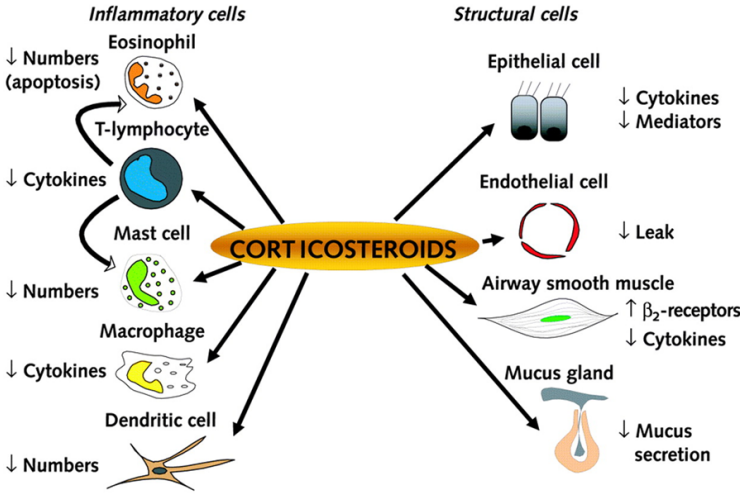
Complications	2008–2011	% des décès
Total live births	7124	
Total deaths	1839	
Overall mortality rate per 1000 live births (95% CI)†	258 (248–268)	
Cause-specific mortality rate per 1000 live births (95% CI)†§		
Congenital anomalies	13 (10–16)	
Respiratory distress syndrome	56 (51–62)	**22%**
Bronchopulmonary dysplasia	12 (10–15)	
Pulmonary: respiratory distress syndrome plus bronchopulmonary dysplasia	68 (63–74)	
Infection	19 (16–22)	7%
Necrotizing enterocolitis	30 (27–34)	12%
CNS injury¶	10 (8–13)	4%
Immaturity	81 (75–88)	31%
Other	34 (30–39)	

Patel et al., NEJM 2015

ANTENATAL STEROIDS

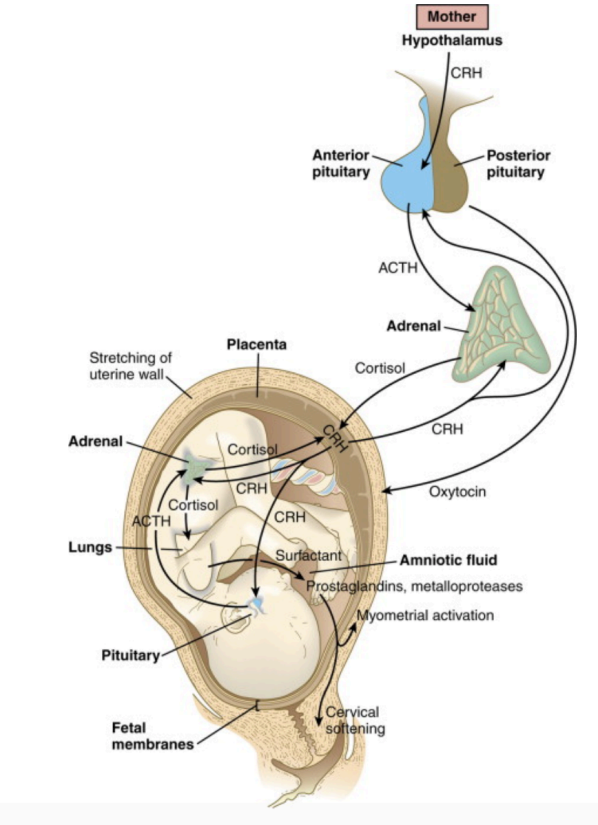
Glucocorticosteroids: a major role in late pregnancy





Braun et al. Endoc. Rev 2013

Glucocorticosteroids: from parturition to lung maturation



Improvment in lung volume after prenatal exposure to corticosteroids

Carlson, Human Embryology and Developmental Biology (Fifth Edition), 2014
Liggins, J Endocr, 1969

Antenatal steroids: a long story of evidence-based medicine

1969 **1972** **1990** **2006** **2017**

The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials

PATRICIA CROWLEY, IAIN CHALMERS, MARC J. N. C. KEIRSE

Revised guidelines
Dosage matter

A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

G. C. Liggins, M.B., Ph.D., F.R.C.O.G., *and* R. N. Howie, M.B., M.R.A.C.P.

J. Endocr. (1969), 45, 515–523
With 1 plate
Printed in Great Britain

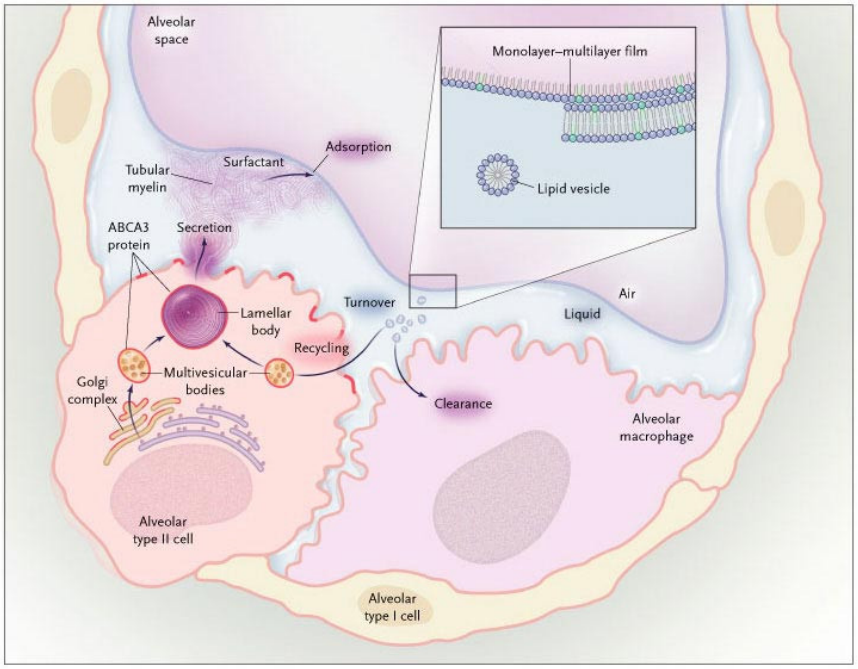
PREMATURE DELIVERY OF FOETAL LAMBS INFUSED WITH GLUCOCORTICOIDS

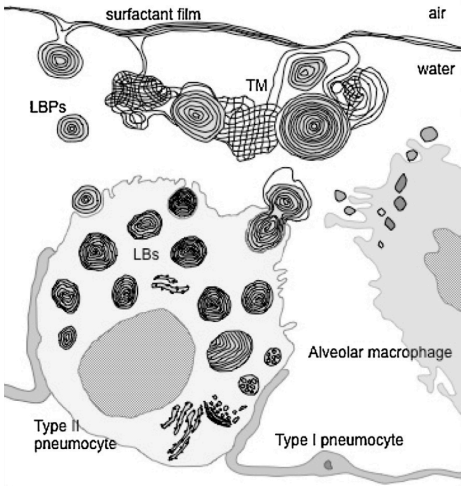
G. C. LIGGINS

Cochrane Library

Cochrane Database of Systematic Reviews

Antenatal steroids and lung maturation

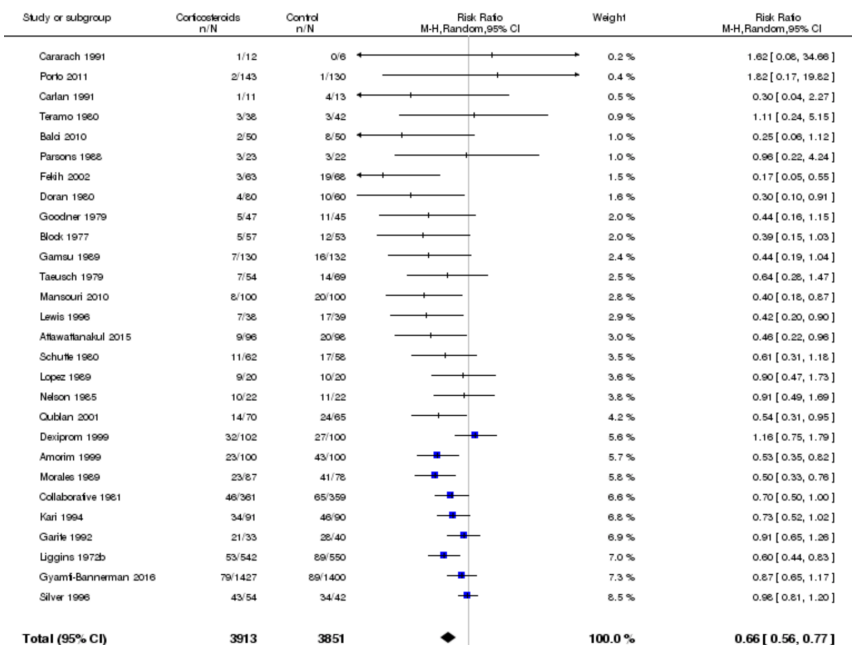




Hallman, NEJM 2004
Olmeda et al., Annals of Anatomy 2017

Antenatal steroids and lung maturation

30 essais cliniques (7774 mères et 8158 enfants)



Study or subgroup	Corticosteroids n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Cararach 1991	1/12	0/6		0.2 %	1.82 [0.08, 34.66]
Porto 2011	2/143	1/130		0.4 %	1.82 [0.17, 19.82]
Carlan 1991	1/11	4/13		0.5 %	0.30 [0.04, 2.27]
Teramo 1980	3/36	3/42		0.9 %	1.11 [0.24, 5.15]
Baldi 2010	2/50	8/50		1.0 %	0.25 [0.06, 1.12]
Parsons 1988	3/23	3/22		1.0 %	0.96 [0.22, 4.24]
Fekih 2002	3/63	19/66		1.5 %	0.17 [0.05, 0.55]
Doran 1980	4/80	10/80		1.6 %	0.30 [0.10, 0.91]
Goodner 1979	5/47	11/45		2.0 %	0.44 [0.16, 1.15]
Block 1977	5/57	12/53		2.0 %	0.39 [0.15, 1.03]
Gamsu 1989	7/130	16/132		2.4 %	0.44 [0.19, 1.04]
Taeusch 1979	7/54	14/69		2.5 %	0.64 [0.28, 1.47]
Mansouri 2010	8/100	20/100		2.8 %	0.40 [0.18, 0.87]
Lewis 1996	7/36	17/39		2.9 %	0.42 [0.20, 0.90]
Attawattanakul 2015	9/96	20/96		3.0 %	0.46 [0.22, 0.96]
Schutte 1980	11/62	17/56		3.5 %	0.61 [0.31, 1.18]
Lopez 1989	9/20	10/20		3.6 %	0.90 [0.47, 1.73]
Nelson 1985	10/22	11/22		3.8 %	0.91 [0.49, 1.69]
Qublan 2001	14/70	24/65		4.2 %	0.54 [0.31, 0.95]
Dexiprom 1999	32/102	27/100		5.6 %	1.16 [0.75, 1.79]
Amorim 1999	23/100	43/100		5.7 %	0.53 [0.35, 0.82]
Morales 1989	23/87	41/78		5.8 %	0.50 [0.33, 0.76]
Collaborative 1981	46/361	65/359		6.6 %	0.70 [0.50, 1.00]
Kari 1994	34/91	46/90		6.8 %	0.73 [0.52, 1.02]
Garite 1992	21/33	28/40		6.9 %	0.91 [0.65, 1.28]
Liggins 1973b	53/542	89/550		7.0 %	0.60 [0.44, 0.83]
Gyamfi-Bannerman 2016	79/1427	89/1400		7.3 %	0.87 [0.65, 1.17]
Silver 1996	43/54	34/42		8.5 %	0.96 [0.81, 1.20]
Total (95% CI)	**3913**	**3851**		**100.0 %**	**0.66 [0.56, 0.77]**

Cochrane Library

Cochrane Database of Systematic Reviews

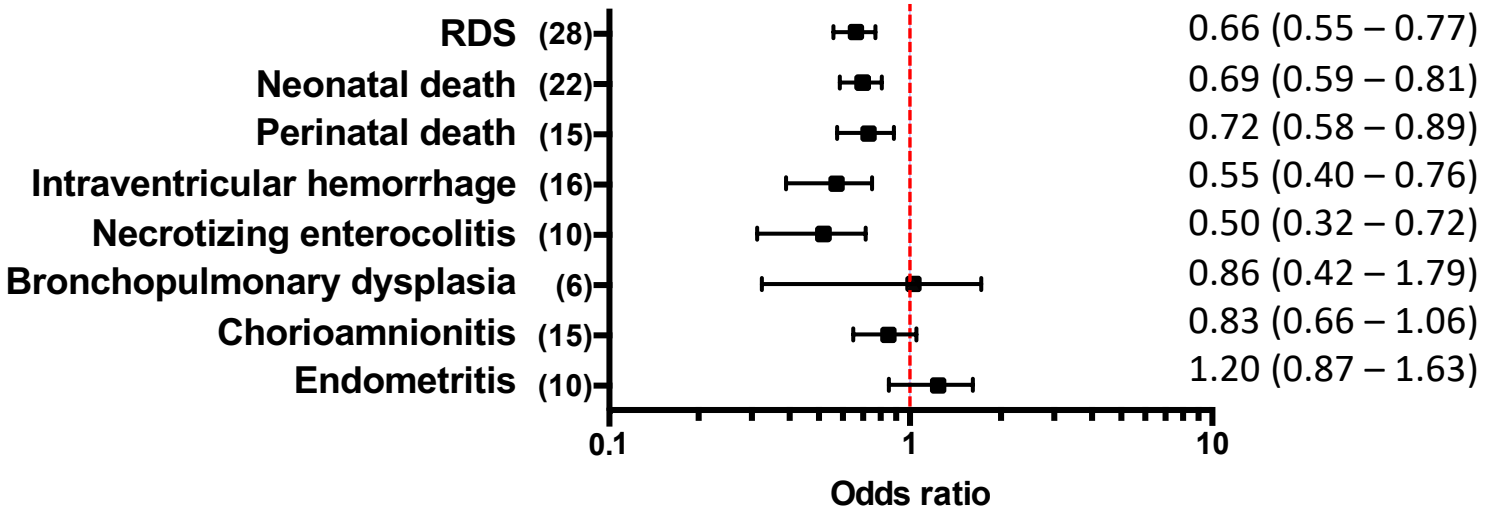
Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

Roberts D, Brown J, Medley N, Dalziel SR

- **<u>RDS</u>:**
  RR 0.66, 95% CI 0.56 to 0.77
  participants = 7764; 28 trials ; I^2 = 48%
- **<u>RDS sévère</u>:**
  RR 0.59, 95% CI 0.38 to 0.91
  participants = 1686; 6 trials ; I^2 = 52%
- **<u>Décès néonatal</u>:**
  RR 0.69, 95% CI 0.59 to 0.81
  participants = 7188 ; 22 trials

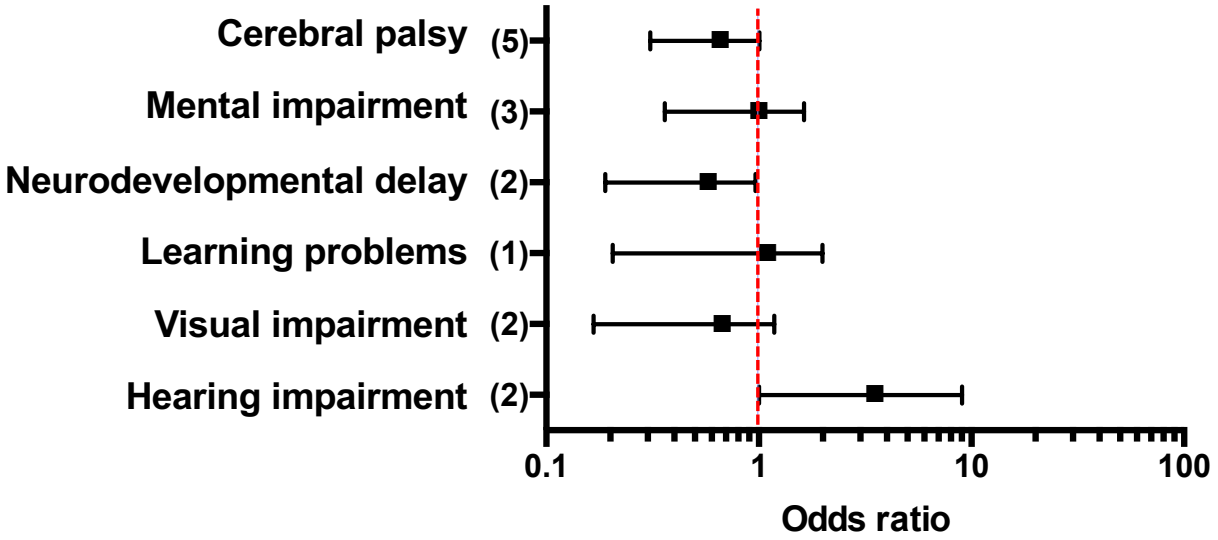
Antenatal steroids and neonatal outcomes

30 clinical trials (7774 mothers & 8158 infants)



Roberts et al., Cochrane Database Syst Rev. 2017

Antenatal steroids and long-term outcomes (3-12y)

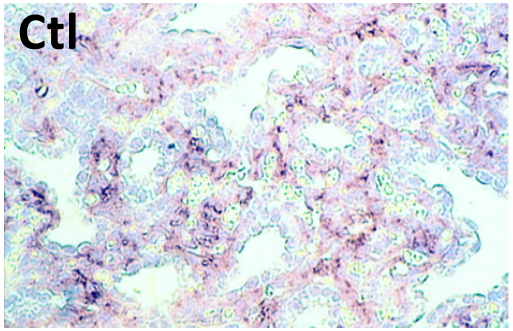


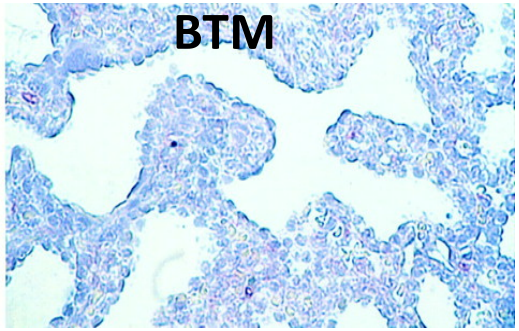
No difference on:

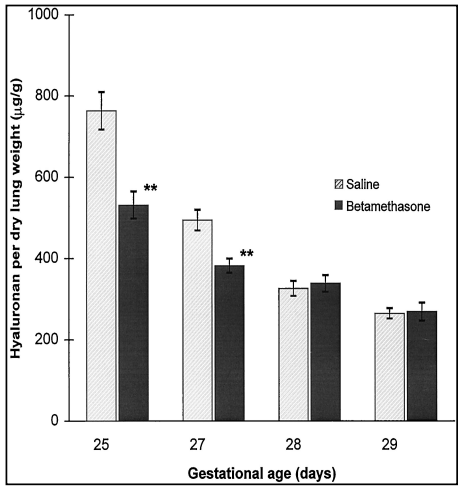
- **Growth**
- **Lung function**
- **Blood pressure**

Roberts et al., Cochrane Database Syst Rev. 2017

Antenatal steroids: potential adverse effects on lungs in animals

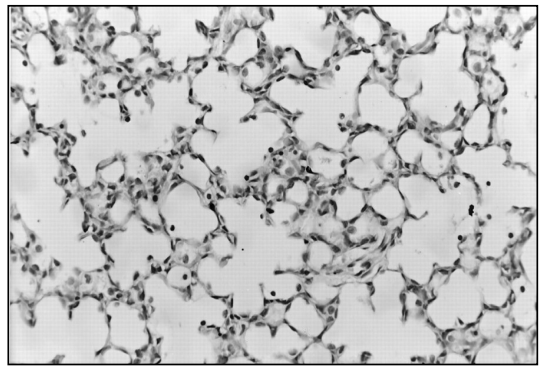


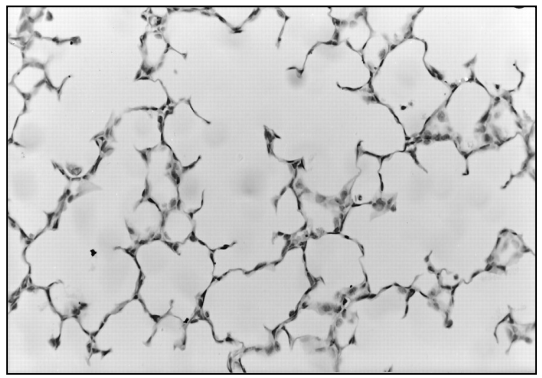




- Significant reduction in hyaluronic acid content after an antenatal dose of BTM
- Maturation-dependent effect
- No impairment of lung weight

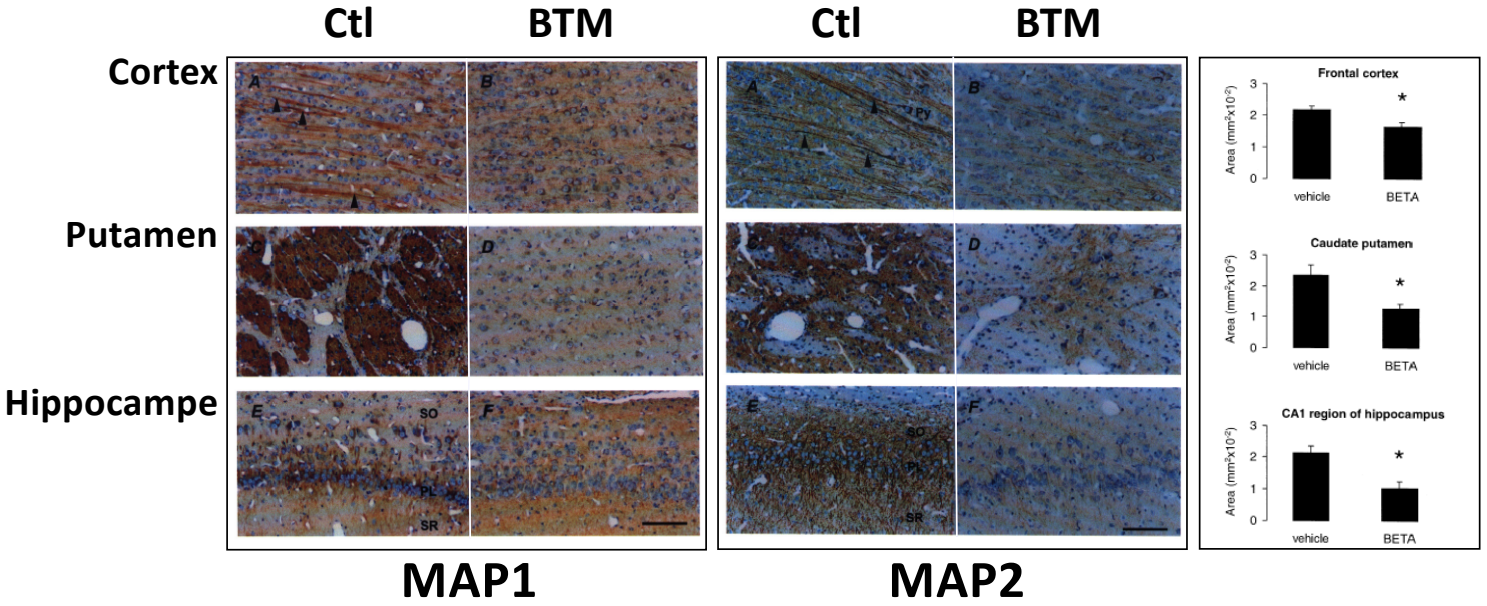
- Endotoxin-like effect of antenatal BTM on lung architecture
- 30% reduction in the total number of alveoli
- Significant thinning of alveolar septa.





Willet et al., Pediatr Res 2000
Johnsson et al., Pediatr Res, 2001

Antenatal steroids: potential adverse effects on brain, in animals



MAP1 **MAP2**

- ↓ **MAP1 in striatum**
- ↓ **MAP2 in striatum and cortex**

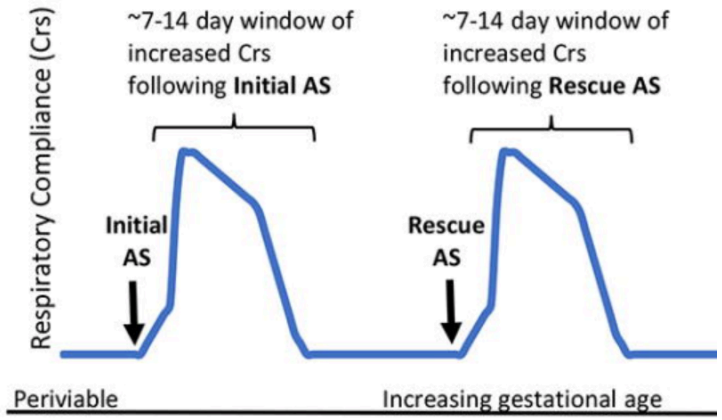
No detectable histological lesion

Correlation between MAP and cerebral blood flow

Schwab et al, J Physiol, 2001

Antenatal steroids: repeated courses, why?

Entry-Delivery Interval	*Betamethasone-Treated Group* *No.*	*RDS*	*% RDS*	*Control Group* *No.*	*RDS*	*% RDS*	*p*
Under 24 hours	29	7	24.1	22	7	31.8	NS
24 and under 48 hours	20	2	10.0	19	7	36.8	NS
2 and under 7 days	28	1	3.6	24	8	33.3	.03
7 days and over	45	1	2.2	32	3	9.4	NS
All live births	122	11	9.0	97	25	25.8	.003
All infants born alive over 24 hours after entry to trial	93	4	4.3	75	18	24.0	.002



Liggins & Howie, Pediatrics 1972
Crowley et al., AJOG, 1995
Jordan et al., J Perinat 2018

Antenatal steroids: repeated courses, effect?

10 RCTs (4733 mothers, 5700 infants)

Benefits:

- -17% RDS
- -16% complications (composite score) within the first week of life

Risks:

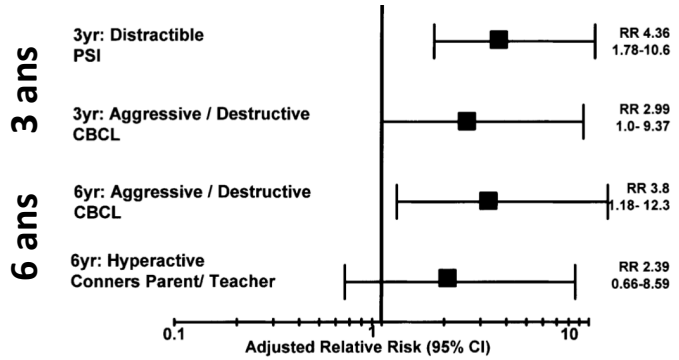
- Reduced birthweight and head circumference
- Conflicting risks for the mothers

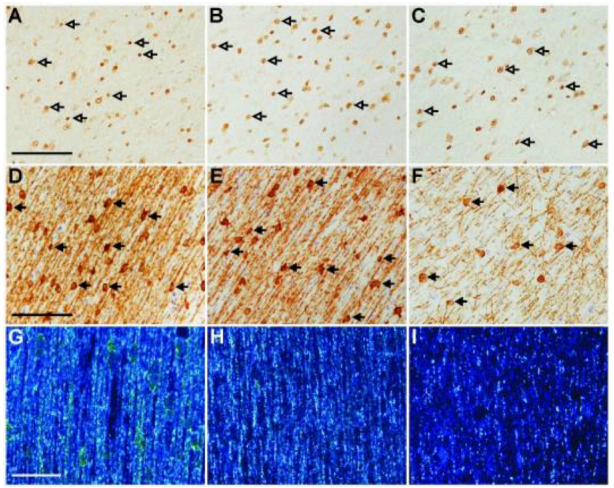
Crowther et al., Cochrane Database Syst Rev. 2015

Antenatal steroids: repeated courses, side effects?

- ***In Baboons***
  - Reduced brain growth
  - Glial activation
  - Delayed myelination

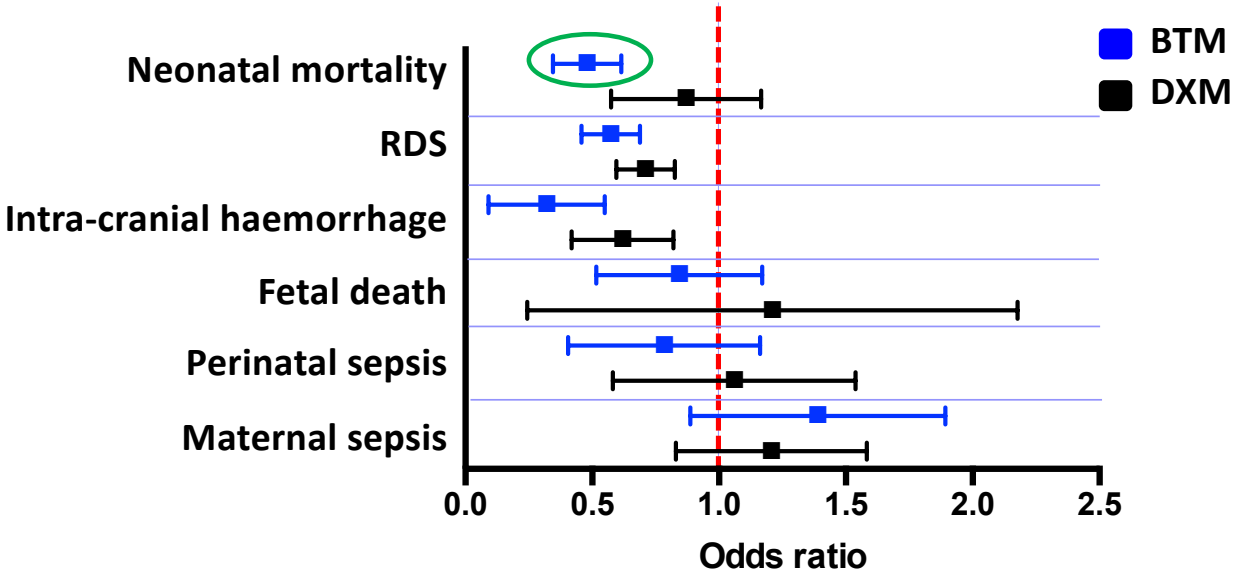
- ***In Humans***
  - Reduced birthweight and HC
  - Abnomal behavioral outcomes





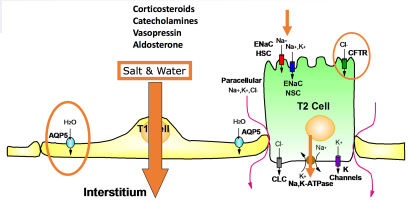
Shields et al. Pediatr Res, 2012
Thorp et al., AJOG, 2004
French et al., AJOG, 1999 & 2004

BTM vs DXM



Jobe & Soll, AJOG, 2004

Antenatal steroids: what about after 34 weeks?



Outcome	Betamethasone (N=1427)	Placebo (N=1400)	Relative Risk (95% CI)	P Value	NNT/NNH
Respiratory distress syndrome	79 (5.5)	89 (6.4)	0.87 (0.65-1.17)	0.36	
Transient tachypnea of the newborn	95 (6.7)	138 (9.9)	0.67 (0.53-0.87)	<0.01	31
Bronchopulmonary dysplasia	2 (0.1)	9 (0.6)	0.22 (0.02-0.92)	0.04	200
RDS/TTN/Apnea	249 (17.8)	198 (13.9)	0.78 (0.66-0.93)	0.004	26
Surfactant use	26 (1.8)	43 (3.1)	0.59 (0.37-0.96)	0.03	77

Hypoglycemia (glucose < 40 mg/dl)	343 (24.0)	209 (14.9)	1.61 (1.38-1.88)	<0.001	5

To be considered according to risk of RDS only

Jain et al., AJP 2007
Gyamfi-Bannerman et al., NEJM, 2016

Antenatal steroids: what about before 24 weeks?

Figure 2. Proportion of Infants Receiving Postnatal Life Support, by Gestational Age at Birth

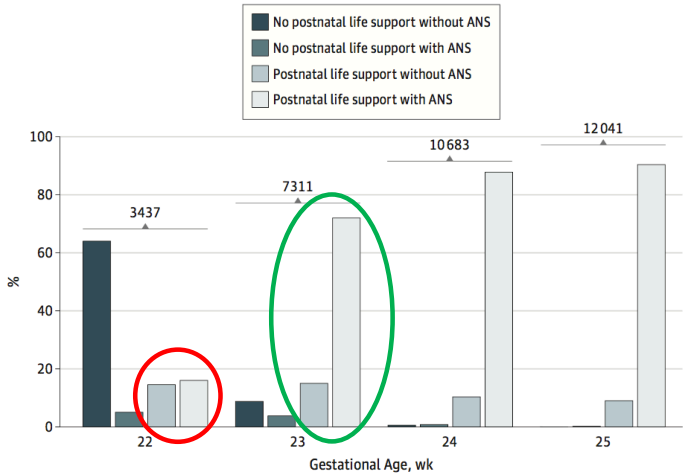


Table 2. Survival Rates, by Gestational Age at Birth

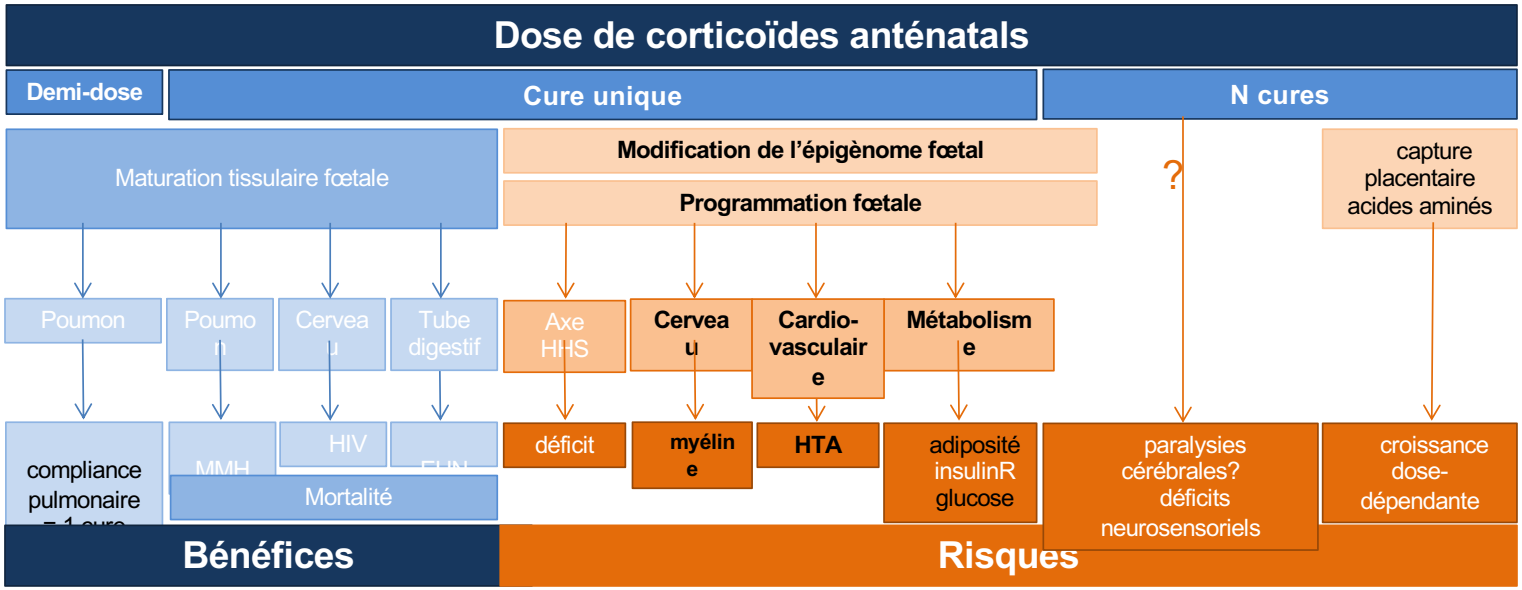
Gestational Age, wk	No. of Survivors/Total No. of Infants (%)		RR (95% CI)	aRR (95% CI)[a]
	Postnatal Life Support Alone	Postnatal Life Support With ANS Exposure		
22	89/503 (17.7)	210/546 (38.5)	2.17 (1.75-2.70)	2.11 (1.68-2.65)
23	391/1097 (35.6)	2884/5210 (55.4)	1.55 (1.43-1.69)	1.54 (1.40-1.70)
24	667/1119 (59.6)	6640/9312 (71.3)	1.20 (1.14-1.26)	1.18 (1.12-1.25)
25	834/1101 (75.7)	8983/10 825 (83.0)	1.10 (1.06-1.13)	1.11 (1.07-1.14)
22-25	1981/3820 (51.9)	18 717/25 892 (72.3)	1.39 (1.35-1.44)	1.37 (1.32-1.42)

Cohort from Vermont Oxford Network (n=29 932)

Improved survival without major handicaps both at 22 and 23 weeks

Ehert et al., JAMA Network Open 2018

Antenatal steroids: does dosage matter?



Trials comparing the commonly used corticosteroids are most urgently needed, as are trials of **dosages** and other variations in treatment regimens

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BETADOSE trial: rationale

- **The current dose derives from sheep experiments in the late 60's and has been unchallenged since 1972**
- **The minimum effective dose to induce fetal lung maturation is unknown**
- **Trials comparing dosages are most urgently needed**
- **Half dose as effective as full dose to induce fetal lung maturation in sheep**

Loehle M, et al. Am J Obstet Gynecol 2010
Schmidt AF, et al. Am J Obstet Gynecol 2018

BETADOSE trial: aims

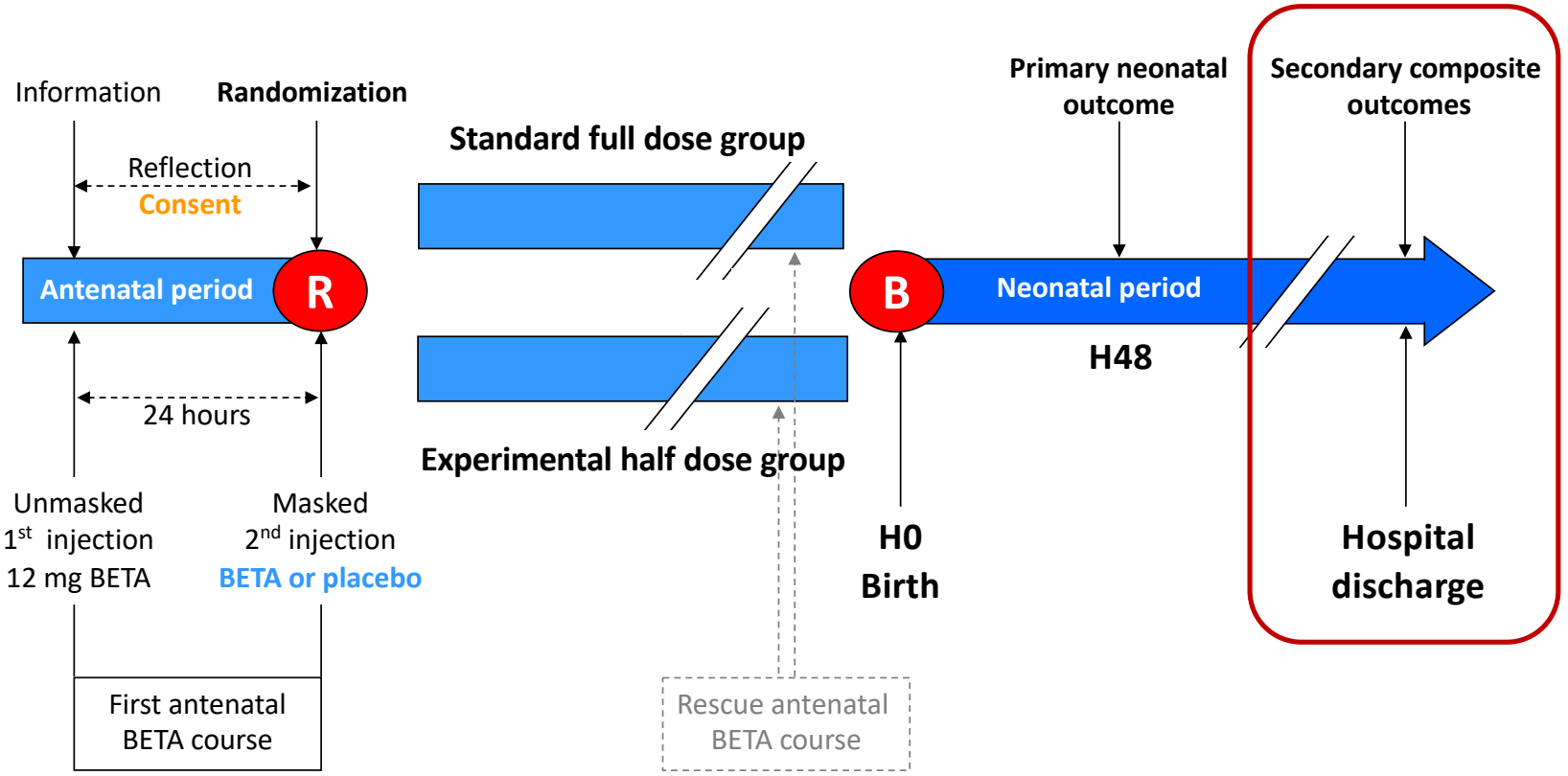
- **Primary aim**: to determine whether half dose regimen given to women at risk of very preterm delivery is not inferior to full antenatal betamethasone dose regimen **to prevent severe RDS**

- **Secondary aims**:
  - to compare other **short-term neonatal complications** between half and full antenatal betamethasone dose regimens
  - to compare **health outcome at discharge** between half and full antenatal betamethasone dose regimens in infants born very preterm

BETADOSE trial: eligibility

- **Inclusion criteria**
  - Age ≥ 18 years
  - Singleton pregnancy
  - First intramuscular betamethasone injection already performed
  - Gestational age < 32 weeks at first betamethasone injection
- **Exclusion criteria**
  - Already received a full course of betamethasone
  - First injection given by the intravascular route
  - In case of preterm labor:
    - Cervical dilatation ≥ 4 cm
    - Ultrasonographic cervical length ≥ 20 mm
  - Chromosomal aberrations and/or major fetal malformations

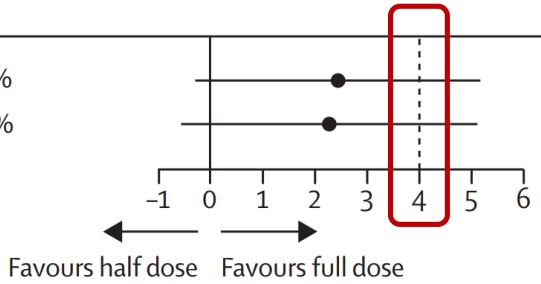
BETADOSE trial: study design



BETADOSE trial: main outcome

Half antenatal betamethasone dose was not found to be noninferior to full antenatal betamethasone dose regimen to prevent severe RDS requiring intra-tracheal surfactant before 48h of life

	Half dose		Full dose		Risk difference (95% CI)
	n/N	%	n/N	%	
Intention-to-treat population	313/1567	20·0%	276/1574	17·5%	2·4% (–0·3 to 5·2)
Per-protocol population	301/1481	20·3%	263/1457	18·1%	2·2% (–0·6 to 5·1)



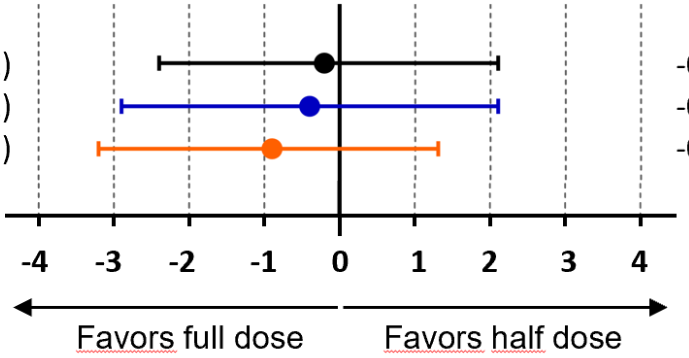
Schhmitz T, et al. Lancet 2022

THE LANCET

BETADOSE trial: secondary outcomes

Survival w/o severe morbidities at discharge (<32 weeks)

Composite outcome*	Half dose n/N (%)	Full dose n/N (%)	Risk difference (95% CI)
A	1386/1559 (88.9)	1395/1566 (89.1)	-0.2 (-2.4 to 2.1)
B	1339/1562 (85.7)	1350/1568 (86.1)	-0.3 (-2.8 to 2.1)
C	1397/1580 (88.4)	1416/1585 (89.3)	-0.9 (-3.2 to 1.3)



Neonatal survival without:

- Severe brain lesions, severe NEC, severe ROP, and moderate-to-severe BPD

Criteria A (**EPIPAGE 2**, Ancel et al. JAMA Ped 2015)

- Severe brain lesions, severe NEC, severe ROP, moderate-to-severe BPD, and proven sepsis

Criteria B (**TIPP trial**, Schmidt et al. NEJM 2001; Bassler et al. Pediatrics 2009)

- Severe brain lesions, postnatal steroids, and surgery

Criteria C (**Victorian Collaborative Network**, Doyle et al. Pediatrics 2001)

Baud et al. AJOG 2024

BETADOSE trial: conclusions

- **Half** dose **did not show non-inferiority** to full antenatal betamethasone dose regimen **to prevent severe RDS**, but:
  - **Survival w/o severe morbidities at discharge was not modified by a 50% betamethasone dose reduction**
  - **Distribution of severe morbidities was similar between the two regimens**
- Results of the **5-year follow-up (ongoing BETANINO study)** are needed before deciding whether reducing antenatal steroids dose is possible

- A course of antenatal corticosteroids given within the seven days prior to preterm birth reduces perinatal and neonatal death and respiratory distress syndrome. [Grade A]
- For women undergoing planned caesarean birth between 37^{+0} and 38^{+6} weeks an informed discussion should take place with the woman about the potential risks and benefits of a course of antenatal corticosteroids. Although antenatal corticosteroids may reduce admission to the neonatal unit for respiratory morbidity, it is uncertain if there is any reduction in respiratory distress syndrome, transient tachypnoea of the newborn or neonatal unit admission overall, and antenatal corticosteroids may result in harm to the neonate which includes hypoglycaemia and potential developmental delay. [Grade B]
- Corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks' gestation in whom imminent preterm birth is anticipated (either due to established preterm labour, preterm prelabour rupture of membranes [PPROM] or planned preterm birth). [Grade A]

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

A correction was published in November 2017 for this title. Click

ACOG COMMITTEE

Number 713 • August 2017 (Replaces
Reaffirmed 2020

Committee on Obstetric Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice in collaboration with committee members Yasser Y. El-Sayed, MD, Ann E.B. Borders, MD, MSc, MPH, and the Society for Maternal–Fetal Medicine's liaison member Cynthia Gyamfi-Bannerman, MD, MSc.

INTERIM UPDATE: This Committee Opinion is updated as highlighted to reflect a limited focused change to clarify that, among specific populations, antenatal corticosteroids should be administered when a woman is at risk of preterm delivery within 7 days.

Antenatal Corticosteroid Therapy for Fetal Maturation

ABSTRACT: Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve newborn outcomes. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. It also may be considered for pregnant women starting at 23 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membrane rupture status and regardless of fetal number. Administration of betamethasone may be considered in pregnant women between 34 0/7 weeks and 36 6/7 weeks of gestation who are at risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who are at risk of preterm delivery within 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Rescue course corticosteroids could be provided as early as 7 days from the prior dose, if indicated by the clinical scenario. Continued surveillance of long-term outcomes after in utero corticosteroid exposure should be supported. Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are encouraged.

Royal College of Obstetricians & Gynaecologists

Antenatal corticosteroids to reduce neonatal morbidity and mortality

Green-top Guideline No. 74
July 2022

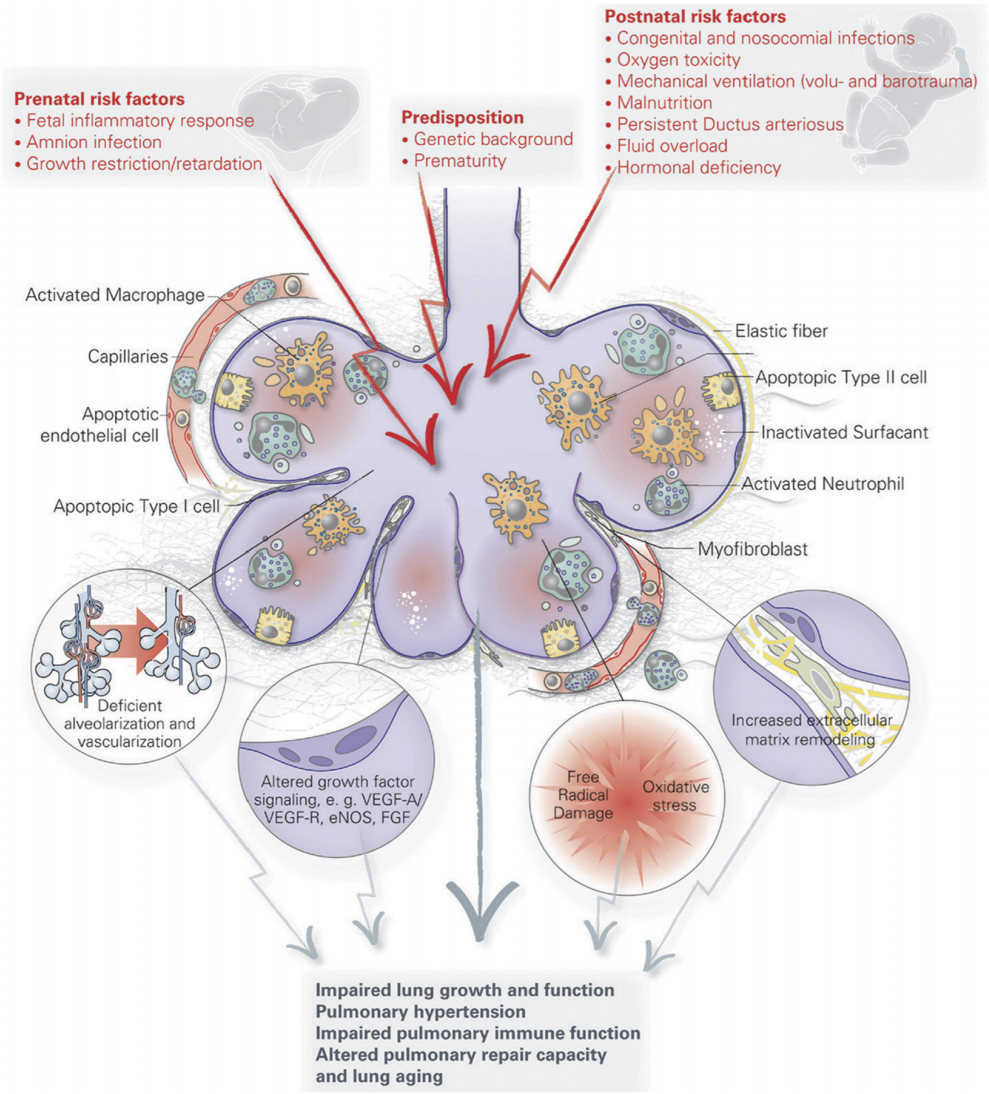
POSTNATAL STEROIDS

BPD in ELGA infants: still a public health issue? (EPIPAGE 2 cohort)

GA	High grade IVH	cPVL	BPD 36w	ROP ≥ 3	NEC
	%	%	%	%	%
<27 weeks	14	2	22	6	5
27-31 weeks	4	2	4	0.3	3
32-34 weeks	0.6	0.8	0.2	0.0	0.9

Ancel et al., JAMA Ped 2015

Lung injury and BPD



inflammation

Reduced angiogenesis / alveolisation

BPD

therapeutic targets

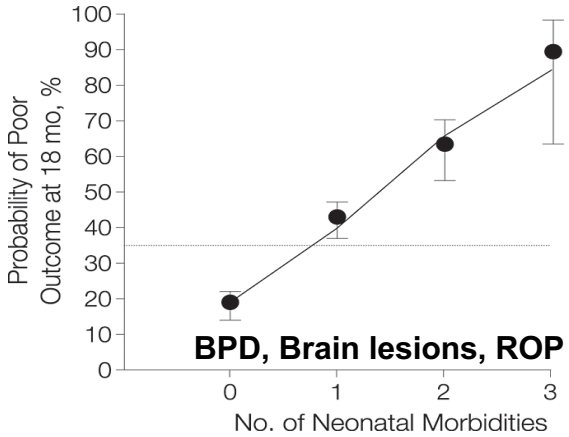
Immature lung

Genetic susceptibility

Speer, 2006; Kinsella, 2006; Jobe, 2001; Collins 2017

Why BPD should be prevented?

- Prolonged hospitalization
- Neurological outcomes:
  - low average IQ (65% of the variance due to BPD and 1% increase associated with 0.15 IQ pt decrease),
  - academic difficulties,
  - delayed speech and language development,
  - visual–motor integration impairments
  - behaviour problems,
  - learning deficits,
  - executive dysfunction
- Pulmonary hypertension
- Chronic pulmonary disease in adults
- Abnormal lung function
- Reduced respiratory reserve
- Cost



Majnemer et al., DMCN, 2000
Eber & Zach, Thorax, 2001
Schmidt et al., JAMA 2003
Doyle, Sem Fetal Neonat Med, 2009
Mazloum et al., Neonatology 2014
Twilhaar et al., JAMA 2018

How could BPD be prevented in the NICU?

- SpO_2 targets
- Cafein citrate
- Late Onset Sepsis prevention
- PDA management
- Gentle ventilation
- Prevention of chronic lung inflammation
- Azythromycin
- Nutrition
- Family-centered care

Effect of DXM treatment in very preterm infants

Cochrane 2021 (Doyle):

Early DXM (< 7d):

Reduction of the combined outcome of mortality or BPD at 36 weeks' PMA
(RR 0.88, 95% CI 0.81 to 0.95; 17 studies, 2791 infants; high-certainty evidence)

Increase of gastrointestinal perforation
(RR 1.73, 95% CI 1.20 to 2.51; 9 studies, 1936 infants; high-certainty evidence)

Increase of cerebral palsy
(RR 1.77, 95% CI 1.21 to 2.58; 7 studies, 921 infants; high-certainty evidence)

Late DXM (≥ 7d):

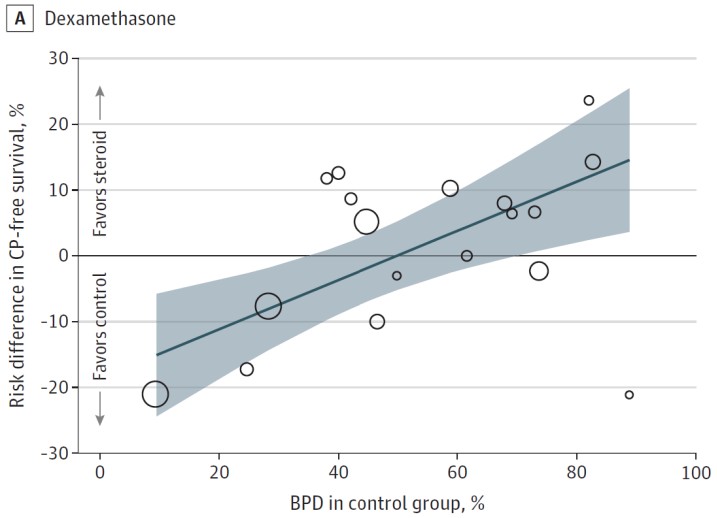
Reduction of the combined outcome of mortality or BPD at 36 weeks' PMA
(RR 0.75, 95% CI 0.67 to 0.84; 12 studies, 553 infants; moderate-certainty evidence)

No effect on the combined outcome of mortality or cerebral palsy
(RR 0.90, 95% CI 0.76 to 1.06; 17 studies, 1290 infants; high-certainty evidence)

Cochrane Database Syst Rev 2021 Nov 11;11(11):CD001145.
Cochrane Database Syst Rev 2021 Oct 21;10(10):CD001146.

Effects of postnatal Dexamethasone on cerebral palsy, among RCTs

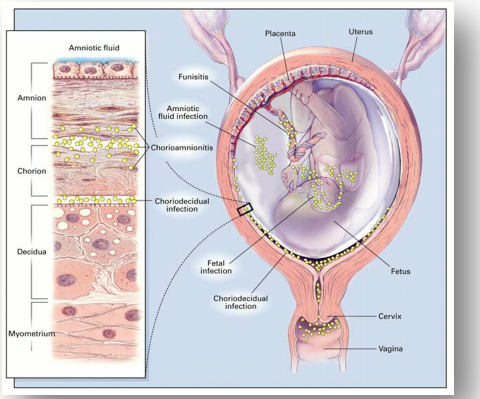
Study or Subgroup	systemic corticosteroids Events	Total	no treatment/comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Early low-dose dexamethasone vs placebo/no treatment						
Romagnoli 1999	2	25	3	25	10.0%	0.67 [0.12 , 3.65]
Sanders 1994	3	19	1	21	3.2%	3.32 [0.38 , 29.23]
Shinwell 1996	39	132	12	116	42.7%	2.86 [1.57 , 5.19]
Sinkin 2000	4	32	1	27	3.6%	3.38 [0.40 , 28.42]
Stark 2001	11	111	12	109	40.5%	0.90 [0.42 , 1.95]
Subtotal (95% CI)		**319**		**298**	**100.0%**	**1.88 [1.24 , 2.86]**
Total events:	59		29			
Heterogeneity: Chi² = 7.34, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 2.95 (P = 0.003)						
1.5.2 Early high-dose dexamethasone vs placebo/no treatment						
Subhedar 1997	0	21	2	21	21.6%	0.20 [0.01 , 3.93]
Yeh 1997	17	132	9	130	78.4%	1.86 [0.86 , 4.02]
Subtotal (95% CI)		**153**		**151**	**100.0%**	**1.50 [0.74 , 3.06]**
Total events:	17		11			
Heterogeneity: Chi² = 2.06, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 1.12 (P = 0.26)						

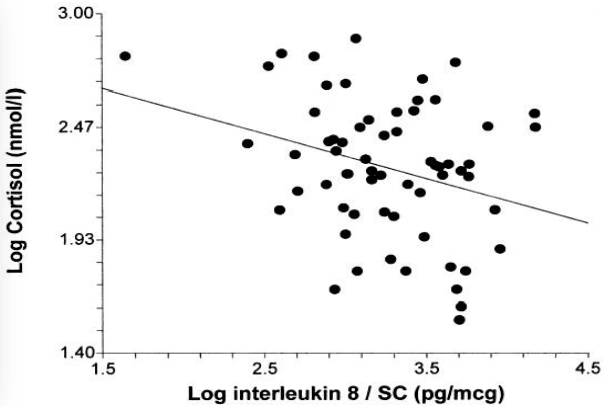


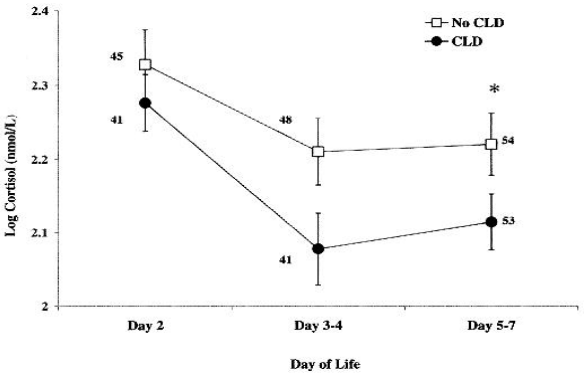
Barrington BMC Pediatrics 2001
Doyle et al., JamaPed 2024
Hay et al., Cochrane CD013730 2023

Drugs for BPD prophylaxis:
physiology first!

Perinatal inflammation → **low Cortisol** → **BPD**





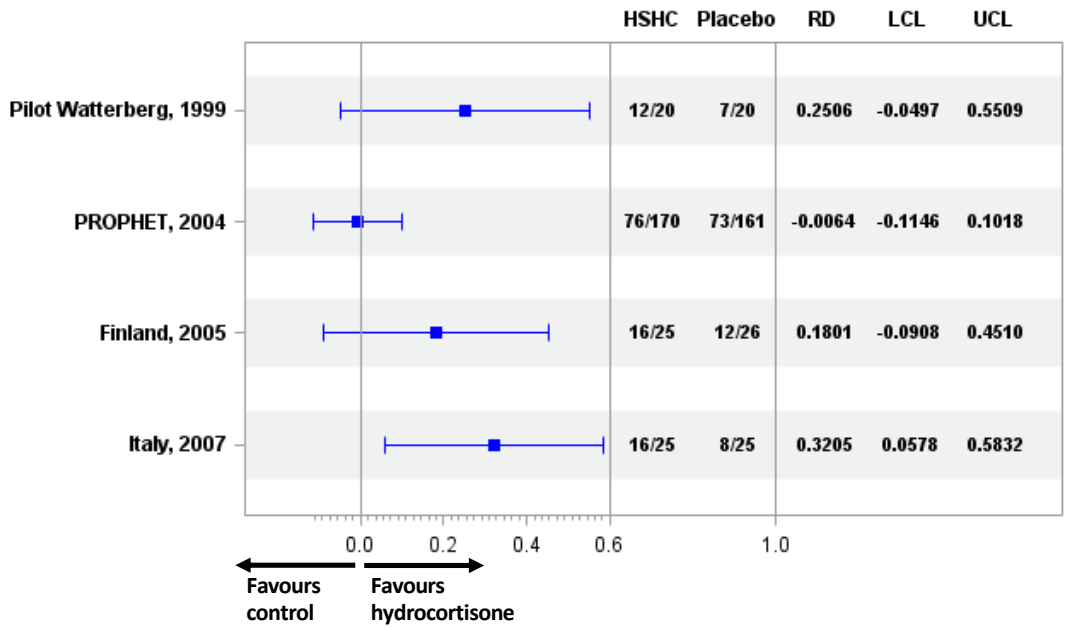


Relative adrenal insufficiency:

-Sickest neonates with high IL8 concentration
-Haemodynamic failure
-PDA
-Infants with subsequent BPD at 36 weeks

Watterberg et al., Pediatrics 2000

Trials using prophylactic hydrocortisone to prevent death or BPD before 2008



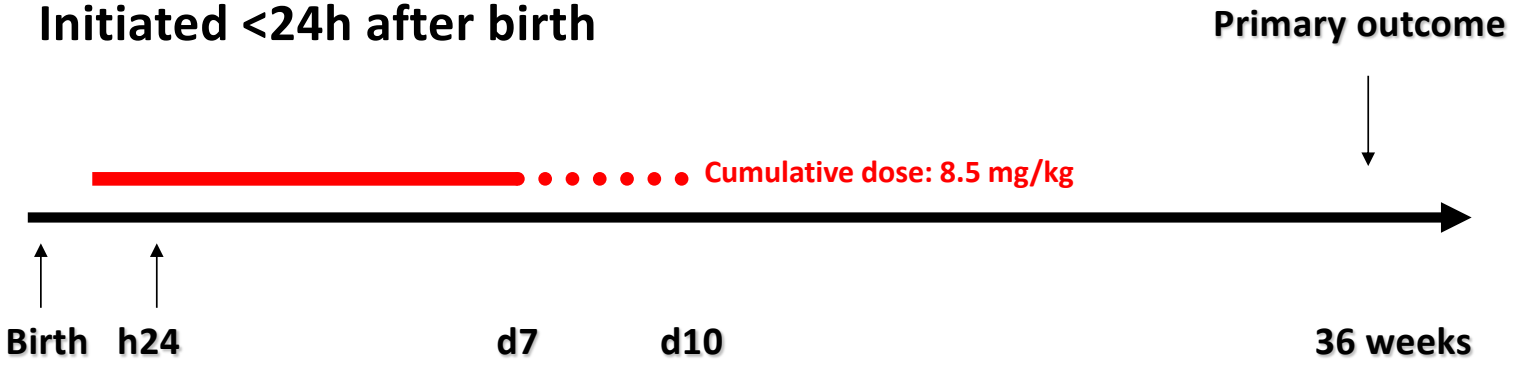
Early closure of the trials !

Watterberg et al., Pediatrics 1999
Watterberg et al., Pediatrics 2004
Peltoniemi et al., J Pediatr 2005
Bonsante et al., Neonatology 2007

PREMILOC study: study design & treatment

- Inborn with GA between 24^{+0} and 27^{+6} weeks without severe IUGR
- A new study design for optimal safety:
  - Lowest hydrocortisone dose,
  - Risk factors of SAE avoided (IUGR/ NSAIs excluded)
  - Interim analyses (triangular design) for better monitoring

0.5 mg/kg/12h during 7 days IV
0.5 mg/kg/24h during 3 days IV
Initiated <24h after birth



PREMILOC study: survival without BPD in ELGA infants

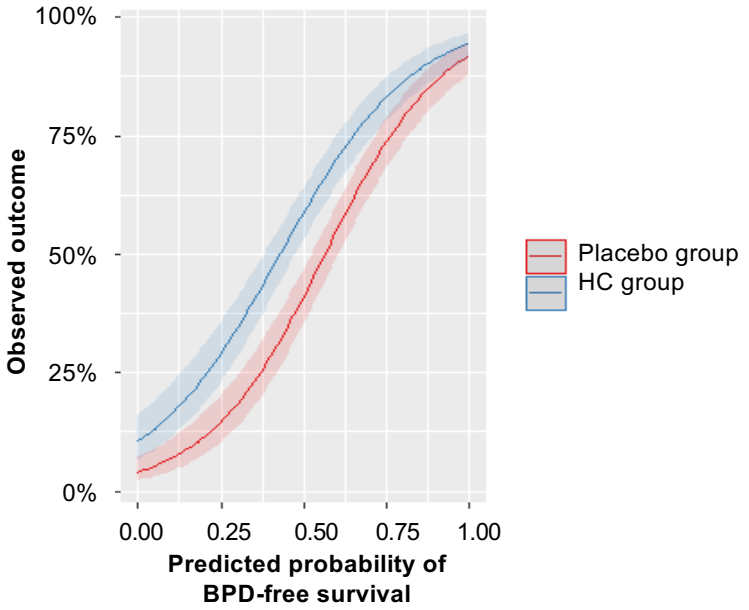
Outcomes	Hydrocortisone N=255	Placebo N=266	OR or SubHR [95% CI]	P value
Primary outcome assessed at 36 weeks PMA– no (%)				
Survival without BPD	**153 (60·0)**	**136 (51·1)**	**1·48 [1·02 ; 2·16]**	**0·04**
Components of primary outcome failure – no (%)				
Death	47 (18·4)	60 (22·6)	0·83 [0·57; 1·21]	0·33
BPD	55 (21·6)	70 (26·3)	0·82 [0·58 ; 1·16]	0·25
Subgroup analysis of the primary outcome – no/total no. (%)				
Births at 24-25 weeks of gestation	28/83 (33·7)	21/90 (23·3)	1·67 [0·86 ; 3·26]	0·13
Births at 26-27 weeks of gestation	125/172 (72·7)	115/176 (65·3)	1·41 [0·89 ; 2·23]	0·14

Baud et al., Lancet 2016

Effect of early HC adjusted on baseline characteristics and subpopulations

	Effect (OR)	Se	95% CI	P-value	Center
Overall estimate	63.6%	28.9%	49.8% to 75.5%	<0.001	0.472
Gestational age	1.504	0.147	1.127 to 2.006	0.006	-
Birthweight	1.006	0.001	1.004 to 1.008	<0.001	-
Female sex	2.843	0.244	1.762 to 4.588	<0.001	-
RSB-moderate	0.389	0.272	0.228 to 0.664	0.001	-
RSB-severe	0.099	0.381	0.047 to 0.208	<0.001	-
Multiple pregnancy	0.475	0.245	0.294 to 0.767	0.002	-
HC treatment	1.820	0.229	1.162 to 2.852	0.009	-

	Effect (OR)	Se	95% CI	P-value
Intercept	0.510	0.168	0.182 to 0.839	0.031
Predict	1.058	0.007	1.045 to 1.071	<.001
HC treatment	2.053	0.230	1.602 to 2.505	0.002
Predict:trt	0.994	0.009	0.976 to 1.012	0.498

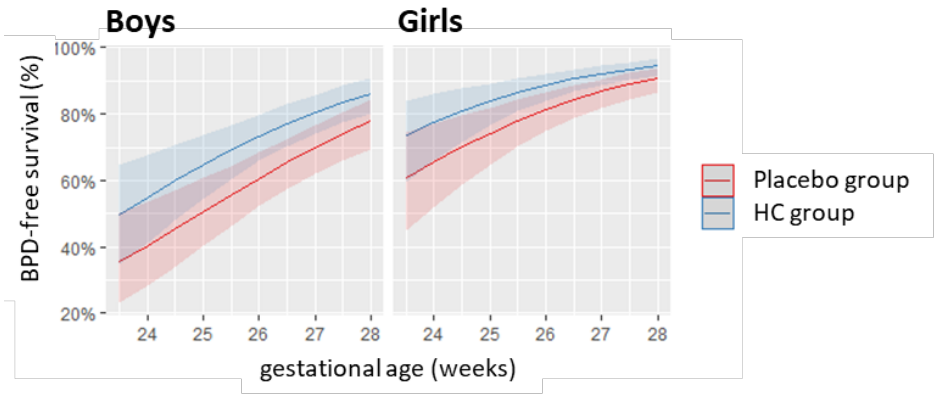


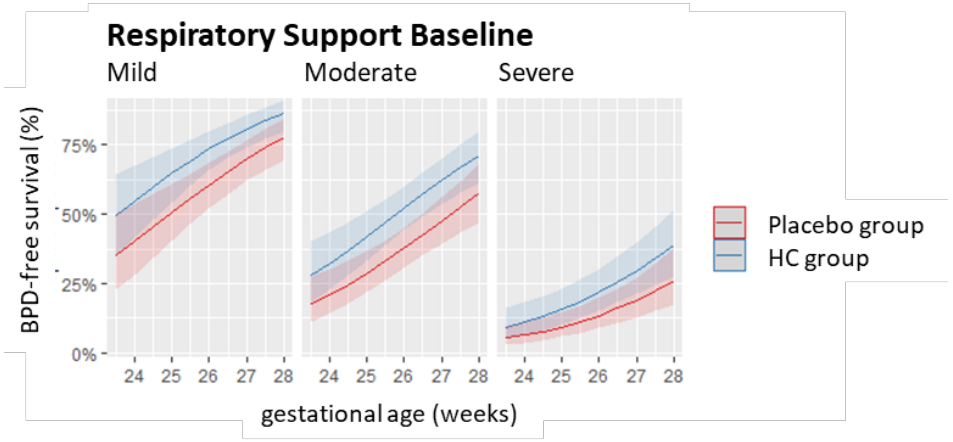
After adjusting for the patient's probability of BPD-free survival using baseline predictors alone, the HC treatment exhibited a highly significant effect (**OR=2.053 [95% CI: 1.602 to 2.501**], p=0.002, with a number needed to treat **NNT=5.81** [4.08 to 23]).

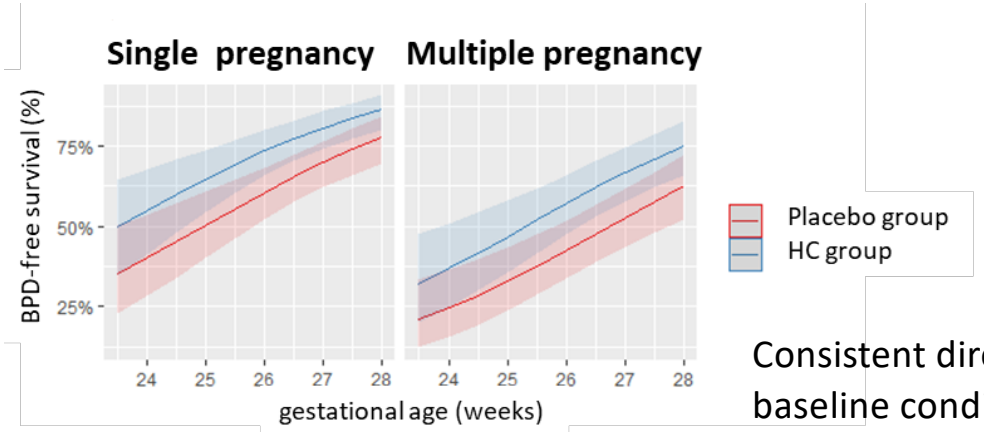
Baud & Lehert, Pediatr Res 2023

Potential interactions

	Odds Ratio (95%CI)	p-value
Gestational age:HC	1.0600 (0.6588 - 1.7057)	0.810
Birthweight:HC	0.9977 (0.9977 - 1.0009)	0.154
Sex:HC	2.4550 (1.0439 - 5.7734)	0.040
RSB:HC	1.2136 (0.6249 - 2.3569)	0.568
Multiple gestation:HC	0.6714 (0.2755 - 1.6357)	0.381







Consistent direction of the treatment effect observed across various baseline conditions, supporting the robustness of the HC treatment in ELGANs

Baud & Lehert, Pediatr Res 2023

Individual Patient Data (IPD) meta-analysis

- 4 RCT (Bonsante, Peltoniemi, Watterberg (Prophet), Baud)
- 982 patients included
- 978 data available
- Adjustment for gestational age, sex and antenatal steroids

- Results comparable with and without adjustment and with further adjustments

Schaeffer et al. J of Pediatr 2019

IPD meta-analysis:

Primary/secondary outcomes adjusted for sex, gestational age, and antenatal steroids

Outcome	Percentage or Mean		Odds Ratio or Mean Difference	95% CI of Odds Ratio or Mean Difference	*P*-value	I^2	NNT
	Hydrocortisone	Placebo					
Survival without BPD at 36w PMA	258/484 (53.3)	225/495 (45.5)	1.45	1.11, 1.90	0.007	0%	13
Death before 36w PMA	79/484 (16.3)	98/495 (19.8)	0.76	0.54, 1.07	0.12	0%	
BPD at 36w PMA	147/405 (36.3)	172/397 (43.3)	0.73	0.54, 0.98	0.038	0%	14
Death before discharge	85/485 (17.5)	112/497 (22.5)	0.70	0.51, 0.97	0.0327	0%	20
Weight at 36w, g	2036 (n=390)	2061 (n=379)	-24.11	-71.36, 23.14	0.32	0%	
Head circumference at 36w, cm	31.0 (n=346)	30.9 (n=337)	0.19	-0.05, 0.42	0.12	0%	
Medical treatment for PDA	202/485 (41.7)	246/497 (49.5)	0.72	0.56, 0.93	0.012	0%	13

Schaeffer et al. J of Pediatr 2019

IPD meta-analysis:

Safety outcomes adjusted for sex, gestational age, and antenatal steroids

Outcome	Percentage or Mean		Odds Ratio or Mean Difference	95% CI of Odds Ratio or Mean Difference	*P*-value	I^2	NNH
	Hydrocortisone	Placebo					
NEC	27/485 (5.57)	29/497 (5.84)	0.95	0.55, 1.63	0.85	19.6%	
GI perforation	35/483 (7.25)	15/497 (3.02)	2.50	1.33, 4.69	0.004	31.9%	24
Late sepsis (bacterial/fungal)	176/485 (36.3)	148/497 (29.8)	1.34	1.02, 1.75	0.0357	0%	15
IVH Grade III/IV	76/477 (15.9)	71/493 (14.4)	1.10	0.76, 1.59	0.60	0%	
Cystic PVL	22/447 (4.92)	25/459 (5.45)	0.89	0.49, 1.60	0.69	0%	
Severe ROP	50/458 (10.9)	54/467 (11.6)	0.92	0.59, 1.45	0.72	0%	

Schaeffer et al. J of Pediatr 2019

Prophylactic HC in the most vulnerable infants:
How baseline cortisol may improve benefits/risks ratio?

- **No NSAI (and acetaminophen?) during the first postnatal 24h**
- **Careful/optimal enteral nutrition, especially in IUGR infants**
- **High baseline cortisol levels (>900 nmol/L) associated with a greater risk of severe IVH and spontaneous intestinal perforation, only in HC-treated infant**

	Hydrocortisone (n=145)		**Placebo (n=163)**	
Severe adverse event	aOR [95%CI]*	p-value	aOR [95%CI]*	p-value
Severe IVH	1.82 [1.06 ; 3.15]	0.03	0.86 [0.47 ; 1.55]	0.61
Periventricular leukomalacia	1.69 [0.45 ; 6.38]	0.43	0.47 [0.18 ; 1.24]	0.13
Necrotizing enterocolitis	1.40 [0.69 ; 2.83]	0.36	0.77 [0.37 ; 1.59]	0.48
Spontaneous intestinal perforation	4.81 [1.34 ; 17.22]	0.02	1.35 [0.57 ; 3.21]	0.50
Severe late-onset sepsis	1.06 [0.72 ; 1.55]	0.78	1.07 [0.71 ; 1.61]	0.74

Renolleau et al. J of Pediatr 2019
Peltoniemi et al., J of Pediatr 2005

Neurological outcomes in the entire population assessed at 22 months of corrected age

% assessed among surviving patients = 93%

Variable	Hydrocortisone (N=194)	Placebo (N=185)
Global neurological assessment – n/N (%)		
No NDI	**141 (73%)**	**130 (70%)**
Mild NDI*	**39 (20%)**	**34 (18%)**
Moderate-to-severe NDI**	**14 (7%)**	**21 (11%)**
Global DQ score – n/N (%)		
>85	**121/158 (77%)**	**110/146 (75%)**
70 – 85	**30/158 (19%)**	**25/146 (17%)**
<70	**7/158 (4%)**	**11/146 (8%)**

*: mild NDI = mild impairment in standardized neurological assessment or global DQ between 70 and 85
**: moderate-to-severe NDI = moderate-to-severe in standardized neurological assessment or global DQ <70

Baud et al., JAMA 2017

Neurological outcomes in the entire population assessed at 22 months of corrected age

% assessed among surviving patients = 93%

Variable	Hydrocortisone (N=194)	Placebo (N=185)
Global Developmental Quotient – median (Q1-Q3)	**92 (86-100)**	**93 (85-100)**
BLR sub-scores – median (Q1 ; Q3)		
Gross motor function	**102 (92-110)**	**103 (91-112)**
Visuo-spatial coordination	**91 (80-101)**	**92 (81-100)**
Langage	**86 (76-95)**	**85 (75-96)**
Sociability	**98 (86-111)**	**95 (84-111)**

Baud et al., JAMA 2017

Neurological outcomes in the entire population assessed at 22 months of corrected age

Variable	Hydrocortisone (N=194)	Placebo (N=185)
Cerebral Palsy – n (%)	12 (6%)	10 (5%)
Hemiplegia – n (%)	1 (<1%)	1 (<1%)
Dyskinesia – n (%)	0	1
Seizures – n (%)	2 (1%)	2 (1%)
Ventricular derivation – n (%)	2 (1%)	2 (1%)
Visual impairment – n (%)	26 (14%)	27 (15%)

Baud et al., JAMA 2017

PREMILOC trial: 2-year neurodevelopmental outcomes (24-25 weekers only)

% assessed among surviving patients = 98%

Variable	Hydrocortisone (N=47)	Placebo (N=49)
BLR scales		
Global DQ score – median [Q1 ; Q3]	**92 [87-100]**	**90 [82-99]**
BLR sub-scores – median [Q1 ; Q3]		
Gross motor function	**102 [95-125]**	**104 [78-114]**
Visuo-spatial coordination	**93 [81-103]**	**87 [77-99]**
Langage	**85 [71-93]**	**84 [67-94]**
Sociability	**98 [88-110]**	**92 [79-110]**

Baud et al. ADC 2018

PREMILOC trial: 5-year neurodevelopmental outcomes

% assessed among surviving patients = 76%

Variables	HC (n=42)[a]	Placebo (n=41)[a]	Crude mean difference (95%CI)	p-value
Primary and secondary outcomes (WPPSI III-IV)				
Mean Full Scale IQ (SD)	N=39 91.9 (13.9)	N=38 86.3 (15.4)	5.7 (-1.01 to 12.33)	0.10
Mean Verbal IQ / Verbal Comprehension Index (SD)	N=40 94.2 (7.5)	N=40 90.3 (17.8)	3.9 (-3.99 to 11.74)	0.33
Mean Performance IQ / Fluid Reasoning Index (SD)	N=41 95.2 (13.4)	N=39 92.2 (14.9)	3.0 (-3.36 to 9.29)	0.36
Mean Visual Spatial Index (SD)	N=39 91.2 (12.4)	N=34 92.9 (12.2)	-1.7 (-7.46 to 4.06)	0.56
Mean Processing Speed IQ / Index (SD)	N=39 93.9 (12.8)	N=39 91.1 (15.2)	2.9 (-3.45 to 9.24)	0.37
Mean Working Memory Index (SD)	N=38 93.0 (9.5)	N=31 88.3 (9.2)	4.7 (0.17 to 9.2)	0.05

Trousson et al. DMCN 2022

PREMILOC trial: 5-year neurodevelopmental outcomes

Variable		OR[9] [IC95%]	p-valeur
Treatment group			
	HC	7.48 [1.76 ; 31.83]	**0.006**
	Placebo	1	
Sex			
	Male	0.79 [0.22 ; 2.81]	0.71
	Female	1	
Chorioamnionitis			
	Yes	0.42 [0.10 ; 1.73]	0.23
	No	1	
BPD @36 weeks			
	Yes	0.61 [0.09 ; 4.02]	0.61
	No	1	
Sepsis			
	Yes	1.51 [0.25 ; 9.26]	0.65
	No	1	
Surgery for PDA			
	Yes	6.44 [0.91 ; 45.79]	0.06
	No	1	
Kidokoro score >6			
	Yes	1	0.36
	No	0.52 [0.13 ; 2.14]	

Multivariate model to predict WPSSI total IQ ≥ 90
(n=56)

Trousson et al. DMCN 2022

Conclusions / take-home messages

- **<u>Prophylactic</u> hydrocortisone in ELGANs is beneficial on:**
  - **Neonatal mortality, BPD at 36 wks PMA, and PDA closure**
  - **The beneficial effect of prophylactic HC was found to be greater when adjusted to baseline risks of BPD or death**
  - **Lack of heterogeneity in the treatment effect in specific subpopulations despite some weak interaction with sex**

Conclusions / take-home messages

- Prophylactic hydrocortisone in ELGANs is beneficial on:
  - Neonatal mortality, BPD at 36 wks PMA, and PDA closure
  - The beneficial effect of prophylactic HC was found to be greater when adjusted to baseline risks of BPD or death
  - Lack of heterogeneity in the treatment effect in specific subpopulations despite some weak interaction with sex

- **2 side effects, with limited impact:**
  - **GI perforation (only seen associated with early Indometacin)**
  - **Secondary sepsis in the most immature infants but without any impact on mortality, BPD, CP, NDI (all reduced by the treatment)**

- **No deleterious effect on neurodevelopment at 2 and 5 years (perhaps some long-term benefits)**

Questions?