Management of Preterm Birth

Piya Chaemsaithong, MD, PhD
Associate Professor
Department of Obstetrics and Gynaecology
Faculty of Medicine Ramathibodi Hospital
Mahidol University

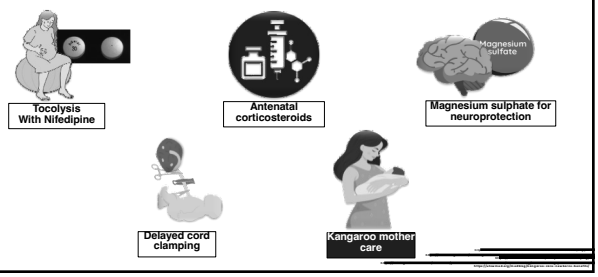
1

Outlines

- Definition
- Causes
- 5 interventions
- Antibiotics, Tocolysis, Steroids, MgSO4, cord clamping
- Prediction and prevention

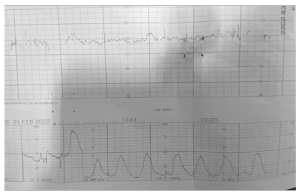
2

5 Interventions to Improve Outcome in Preterm Labor with Intact Membranes



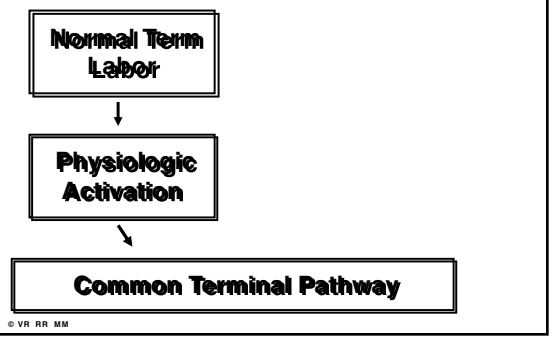
3

Clinical Presentation of Term and Preterm Labor are Similar

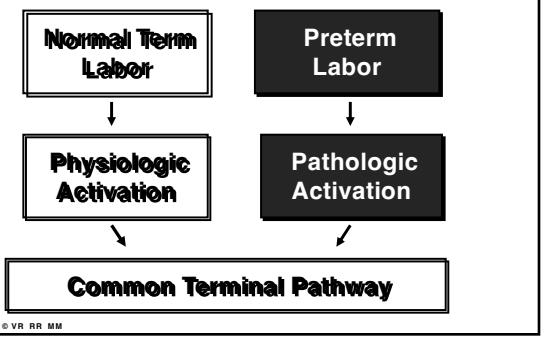


Regular uterine contractions

4



5



6

Solution

To Stop Uterine Contractions with Tocolytics

7

To treat uterine contractions: To treat preterm labor


Pethidine

Nifedipine


Terbutaline


MgSO4


Indomethacin

8

Tocolytic Agents

- Decrease the frequency of contractions temporarily
- Do not decrease the rate of preterm delivery or neonatal morbidity

Wilson A, Hodgetts-Morton VA, Marson EJ, Markland AD, Larkai E, Papadopoulou A, Coomarasamy A, Tobias A, Chou D, Oladapo OT, Price MJ, Morris K, Gallos ID. Tocolytics for delaying preterm birth: a network meta-analysis (NMA). Cochrane Database Syst Rev. 2022 Aug 10;8(8):CD014676

9

Why ?

Preterm uterine contractions are not the <u>cause of preterm labor,</u> but the clinical manifestations of a pathologic insult

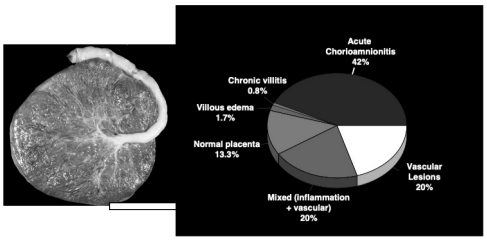
10

Preterm Birth is <u>Not a Physiologic Event</u>

www.lilaussieprems.com.au-.

11

Placental Pathology in Prematurity



Arias et al. Obstet Gynecol 1997;69:285.

12

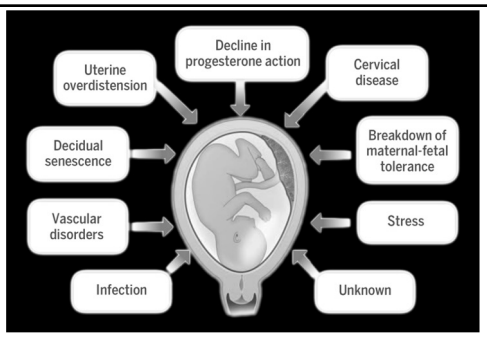
REVIEW

Preterm labor: One syndrome, many causes

Roberto Romero,[1,2,3]* Sudhansu K. Dey,[4] Susan J. Fisher[5]

Romero R, Dey SK, Fisher SJ. Science. 2014;345:760-5.

13



Romero R, Dey SK, Fisher SJ. Science. 2014;345:760-5.

14

Definition of preterm birth

- Delivery before 37 completed weeks
- Delivery ≥ $20^{0/7}$ weeks – $36^{6/7}$ weeks
- Threshold of viability lies between 20-26 weeks of gestation
- **Threshold of viability Thailand (RTCOG): At least 24/07 weeks of gestation, birth weight ≥500

·William Obstetrics, 26th Edition
·ACOG No. 171

15

Definition of preterm birth



Extremely preterm birth	Early preterm	Late preterm
< 28 complete weeks	<$33^{6/7}$ weeks	34-36 weeks

Williams Obstetrics, 26th ed. New York: McGraw-Hill; 2022.

16

Diagnosis of preterm labor

Regular Uterine Contraction ✚ Cervical Progression ✚ Before GA 37 weeks

Williams Obstetrics, 26th ed. New York: McGraw-Hill; 2022.

17

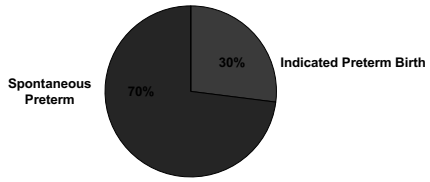
Diagnosis of preterm labor

• Threatened Preterm Labor	· Regular uterine contraction without cervical progression
• Braxton Hicks Contractions (False labor pain)	· Irregular uterine contraction without cervical progression

Williams Obstetrics, 26th ed. New York: McGraw-Hill; 2022.

18

Preterm Birth – Indicated vs. Spontaneous



Spontaneous Preterm Labor + Preterm PROM => 65-70% of Preterm births

Goldenberg RL, Culhane JF, Iams JD, Romero R. *Lancet* 2008;371:75-84

19

Management of Preterm Labor

20

Tocolysis

21

To treat uterine contractions: To treat preterm labor

22

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

OPEN ACCESS

David M Haas *associate professor of obstetrics and gynecology*[1], Deborah M Caldwell *MRC fellow population health science*[2], Page Kirkpatrick *research associate*[1], Jennifer J McIntosh *medical resident*[1], Nicky J Welton *MRC research fellow*[2]

[1]Department of Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, USA; [2]School of Social and Community Medicine, University of Bristol, Bristol, UK

- Design: Systematic review and network meta-analysis, Study selection: Randomized controlled trials of tocolytic therapy in women at risk of preterm delivery
- Results: 95 randomized controlled trials of tocolytic therapy were reviewed
- Short-term benefit
  - Increases the likelihood of delaying delivery ≥48 hours
  - No significant reduction in preterm birth rate or improvement in major neonatal outcomes
- Neonatal outcome
  - CCB and Oxytocin receptor antagonists are associated with
    - Decreased respiratory distress syndrome
    - Decreased NICU admission
    - Better neonatal outcome profile

23

Tocolysis drugs

Dosage	Contraindication	Side effects
Loading: · Adalat(10) 1 tab PO q 15 min x 4 · Adalat(10) 2 tab q 30 min x 3 Maintenance: · Control release 60-160 mg/d · 20-40 mg PO q 6-8 hr (max 160 mg/d)	· Hypotension · Combined with MgSO4 > enhanced neuromuscular blocking effect > pulmonary and cardiac failure	· Transient hypotension · Transient tachycardia · Flushing · Headache, dizziness · Nausea

Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

24

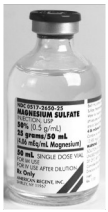
Tocolysis drugs

Dosage	Contraindication	Side effects
Continuous IV infusion: • Terbutaline 0.25 mg IV slowly push then maintenance 2 mg in 5%Dn/2 100 ml IV 10-25 mcg/min q 20-30 min (Max 25 mcg/min)	• Cardiac arrhythmia • Uncontrolled DM • Hyperthyroidism	• Tachycardia • Tachyarrhythmia • Hypotension • Myocardial infarction • Pulmonary edema • Hyperglycemia • Hypokalemia • Nausea • Headache • Tremor

Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

25

Tocolysis drugs



Dosage	Contraindication	Side effects
• 10%MgSO4 4 g IV slowly push in 20 min then 50% MgSO4 40 g + 5%Dn/2 1000ml IV rate 50 ml/hr (2 g/hr)	• Myasthenia gravis • Renal disease	• Flushing, headache, nausea • Lethargy • Pulmonary edema • Toxicity: absent, respiratory depression, cardiac arrest

Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

26

Tocolysis drugs

Dosage	Contraindication	Side effects
• 50 mh PO then 25-50 mg PO q 6 hr (max 200 mg/day)	• NSAIDs allergy • Peptic ulcer disease	• Premature closure of ductus arteriosus in third trimester • Oligohydramnios (limited use 24-48 hr)

Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

27

Magnesium Sulfate for Neuroprotection

28

Magnesium Sulfate for Neuroprotection

Magnesium sulphate

Neuroprotection and Cerebral Palsy

https://www.rxwiki.com/50-magnesium-sulfate-injection-500-mgml-single-dose-vial-10-ml

29

www.AJOG.org Obstetrics REVIEWS

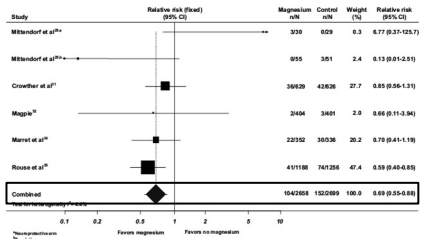
Antenatal magnesium sulfate for the prevention of cerebral palsy in preterm infants less than 34 weeks' gestation: a systematic review and metaanalysis

Agustín Conde-Agudelo, MD, MPH; Roberto Romero, MD

Conde-Agudelo A, Romero R. Am J Obstet Gynecol. 2009;200(6):595-609.

30

Antenatal magnesium sulfate was associated with a significant reduction in the risk of cerebral palsy



Conde-Agudelo A, Romero R. Am J Obstet Gynecol. 2009;200(6):595–609

31

Magnesium sulfate administered to women at risk of delivery before 34 weeks of gestation reduces the risk of cerebral palsy

	Relative risk (95% CI)
Cerebral palsy	0.69 (0.55-0.88)
Moderate/severe cerebral palsy	0.64 (0.44-0.92)
Mild cerebral palsy	0.74 (0.52-1.04)
Total pediatric mortality	1.01 (0.89-1.14)
Fetal mortality	0.78 (0.42-1.46)
Death or cerebral palsy	0.692 (0.83-1.02)

No overall difference in the risk of total pediatric mortality

May RW, Walters AGB, Gamble GD, Crowther CA, Dalziel SR, Eagleton CL, McKinlay CJD, Milne BJ, Harding JE. PLoS Med. 2025 May 28;22(5):e1004618

32

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 28, 2008 VOL. 359 NO. 9

A Randomized, Controlled Trial of Magnesium Sulfate for the Prevention of Cerebral Palsy

Dwight J. Rouse, M.D., Deborah G. Hirtz, M.D., Elizabeth Thom, Ph.D., Michael W. Varner, M.D., Catherine Y. Spong, M.D., Brian M. Mercer, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D., Yoram Sorokin, M.D., James M. Alexander, M.D., Margaret Harper, M.D., John M. Thorp, Jr., M.D., Susan M. Ramin, M.D., Fergal D. Malone, M.D., Marshall Carpenter, M.D., Menachem Miodovnik, M.D., Atef Moawad, M.D., Mary J. O'Sullivan, M.D., Alan M. Peaceman, M.D., Gary D.V. Hankins, M.D., Oded Langer, M.D., Steve N. Caritis, M.D., and James M. Roberts, M.D., for the Eunice Kennedy Shriver NICHD Maternal–Fetal Medicine Units Network*

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med. 2008 Aug 28;359(9):895-905

33

Methods

- **Multicenter, placebo-controlled, double-blind**
- **Women at imminent risk for delivery between 24 and 31 weeks of gestation**
  - **Magnesium sulfate, administered intravenously as a 6-g bolus followed by a constant infusion of 2 g per hour**
  - **placebo**
- **The primary outcome: composite of stillbirth or infant death by 1 year of corrected age or moderate or severe cerebral palsy at or beyond 2 years of corrected age**

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med. 2008 Aug 28;359(9):895-905

34

Moderate or severe cerebral palsy occurred significantly less frequently in the magnesium sulfate group

Outcome	Magnesium Sulfate (N=1041)	Placebo (N=1095)	Relative Risk (95% CI)	P Value
	no./total no. (%)			
All pregnancies				
Moderate or severe cerebral palsy or death*	118/1041 (11.3)	128/1095 (11.7)	0.97 (0.77–1.23)	0.80
Moderate or severe cerebral palsy alone	20/1041 (1.9)	38/1095 (3.5)	0.55 (0.32–0.95)	0.03
Death alone	99/1041 (9.5)	93/1095 (8.5)	1.12 (0.85–1.47)	0.41
Pregnancies without major congenital anomalies				
Moderate or severe cerebral palsy or death*	100/997 (10.0)	117/1063 (11.0)	0.91 (0.71–1.17)	0.47
Moderate or severe cerebral palsy alone	18/997 (1.8)	34/1063 (3.2)	0.56 (0.32–0.99)	0.04
Death alone	83/997 (8.3)	86/1063 (8.1)	1.03 (0.77–1.37)	0.85
Scores on the Bayley Scales of Infant Development				
Psychomotor Development Index <70	134/876 (15.3)	144/919 (15.7)	0.98 (0.79–1.21)	0.83
Psychomotor Development Index <85	299/876 (34.1)	315/919 (34.3)	1.00 (0.88–1.13)	0.95
Mental Development Index <70	165/876 (18.8)	171/919 (18.6)	1.01 (0.83–1.23)	0.90
Mental Development Index <85	406/876 (46.3)	427/919 (46.5)	1.00 (0.90–1.10)	0.96

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med. 2008 Aug 28;359(9):895-905

35

The risk of death did not differ significantly between the groups (relative risk, 1.12; 95% CI: 0.85 to 1.47). No woman had a life-threatening event

Variable	Magnesium Sulfate (N=1096)	Placebo (N=1145)	P Value
Obstetrical outcomes			
Gestational age at delivery — wk	29.8±3.1	29.7±3.1	0.32
Receipt of antenatal corticosteroids — no. (%)	1062 (96.9)	1116 (97.5)	0.49
Chorioamnionitis — no./total no. (%)	127/1086 (11.7)	131/1141 (11.5)	0.88
Cesarean delivery — no./total no. (%)	417/1086 (38.4)	448/1141 (39.3)	0.68
Endometritis — no./total no. (%)	74/1086 (6.8)	80/1141 (7.0)	0.85
Pulmonary edema — no./total no. (%)	8/1086 (0.7)	3/1141 (0.3)	0.11
Adverse events†			
Any adverse event — no./total no. (%)	833/1078 (77.3)	140/1125 (12.4)	<0.001
Flushing — no./total no. (%)	703/1078 (65.2)	74/1125 (6.6)	<0.001
Sweating — no./total no. (%)	307/1078 (28.5)	28/1125 (2.5)	<0.001
Pain or burning at intravenous site — no./total no. (%)	259/1078 (24.0)	29/1125 (2.6)	<0.001
Nausea or vomiting — no./total no. (%)	166/1078 (15.4)	19/1125 (1.7)	<0.001
Respiratory depression — no./total no. (%)‡	7/1078 (0.6)	3/1125 (0.3)	0.22
Infusion stopped because of adverse event — no./total no. (%)	45/1078 (4.2)	16/1125 (1.4)	<0.001

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med. 2008 Aug 28;359(9):895-905

36

Conclusions

Fetal exposure to magnesium sulfate before anticipated early preterm delivery did not reduce the combined risk of moderate or severe cerebral palsy or death, although the rate of cerebral palsy was reduced among survivors

Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, Iams JD, Wapner RJ, Sorokin Y, Alexander JM, Harper M, Thorp JM Jr, Ramin SM, Malone FD, Carpenter M, Miodovnik M, Moawad A, O'Sullivan MJ, Peaceman AM, Hankins GD, Langer O, Caritis SN, Roberts JM; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. N Engl J Med. 2008 Aug 28;359(9):895-905

37

Magnesium sulphate

Reduces cerebral palsy

Improve Gross Motor Skill

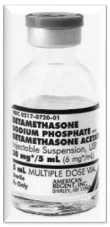
https://www.vectorstock.com/royalty-free-vector/cerebral-palsy-line-color-line-icon-vector-53186807
https://www.shutterstock.com/search/motor-skills-icon

38

Antenatal Corticosteroid

39

Antenatal corticosteroids



Betamethasone

Dexamethasone

40

Beneficial Effect of Antenatal Corticosteroids

	Risk ratio	95% CI
Perinatal death	0.85	0.77-0.93
Neonatal death	0.78	0.70-0.87
Respiratory distress syndrome	0.71	0.65-0.78
Intraventricular hemorrhage	0.58	0.45-0.75
Developmental delay in childhood	0.51	0.27-0.97
Chorioamnionitis	0.86	0.69-1.08
Endometritis	1.14	0.82-1.58

McGoldrick E, Stewart F, Parker R, et al. Cochrane Database Syst Rev. 2020;12(12):CD004454.

41

Adverse Effects of Antenatal Corticosteroid

Lower density of neurons in the hippocampus

Less birth weight and smaller head circumference

More moderate or severe neurologic disabilities

Lucovnik M, Chambliss LR, Garfield RE. Am J Obstet Gynecol. 2013 Sep;209(3):217.e1-3

42

Effects of Antenatal Glucocorticoid Therapy on Hippocampal Histology of Preterm Infants

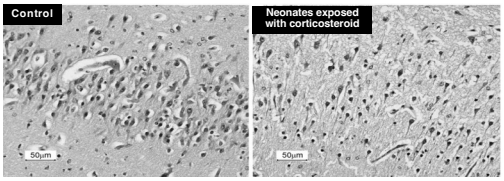
Deodata Tijsseling[1,*], Lia D. E. Wijnberger[2,*], Jan B. Derks[1], Cindy T. J. van Velthoven[3], Willem B. de Vries[1], Frank van Bel[1], Peter G. J. Nikkels[4], Gerard H. A. Visser[1]

- 21 Neonates
- Gestational age: 24-32 weeks of gestation
- Died within 4 days after delivery
- Underwent brain autopsy to examine for the presence or absence of large and small neurons in regions of the hippocampus

Tijsseling d, et al. Effects of antenatal glucocorticoid therapy on hippocampal histology of preterm infants 2012

43

Hippocampi in the Antenatal Glucocorticoids Group Showed a Lower Density of Large Neurons and Neurons Irrespective of Size



Antenatal corticosteroids treatment	Score large neurons	p value	Score neurons irrespective of size	p value
No antenatal corticosteroids	4 (3 – 4)	0.01	3 (3-3.8)	0.02
antenatal corticosteroids	2 (203)		2.55 (2-3)	

Tijsseling d, et al. Effects of antenatal glucocorticoid therapy on hippocampal histology of preterm infants 2012

44

Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial

Kellie E Murphy, Mary E Hannah, Andrew R Willan, Sheila A Hewson, Arne Ohlsson, Edmond N Kelly, Stephen G Matthews, Saroj Saigal, Elizabeth Asztalos, Susan Ross, Marie-France Delisle, Kofi Amankwah , Patricia Gusedle, Amiram Gafni, Shoo K Lee, B Anthony Armson, for the MACS Collaborative Group*

Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

45

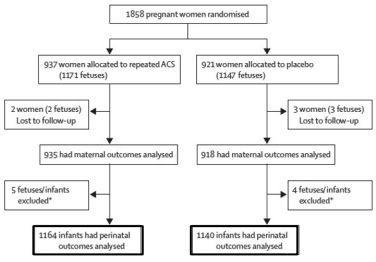
Method

- Whether multiple courses of antenatal corticosteroids would reduce neonatal morbidity and mortality without adversely affecting fetal growth
- Women at 25-32 weeks' gestation who remained undelivered 14-21 days after an initial course of antenatal corticosteroids (n=1,858)
  - randomly assigned to
    - multiple courses of antenatal corticosteroids (n=937); every 14 days until week 33 or delivery
    - placebo (n=921),
- The primary outcome: a composite of perinatal or neonatal mortality, severe respiratory distress syndrome, intraventricular hemorrhage (grade III or IV), periventricular leucomalacia, bronchopulmonary dysplasia, or necrotizing enterocolitis

Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

46

Methods



Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

47

Infants exposed to multiple courses of antenatal corticosteroids had similar morbidity and mortality to those exposed to placebo (12.9%) vs. (12.5%)

	Antenatal corticosteroid (n=1164)	Placebo (n=1140)	Mean difference (95% CI)	P value
Composite primary outcome	13%	13%	1.04 (0.77-1.39)	0.83
Stillbirth or neonatal death ≤28 days after birth or before discharge	4%	4%	1.08 (0.67-1.66)	0.82
Severe RDS	8%	7%	1.14 (0.80-1.58)	0.51
Bronchopulmonary dysplasia	2%	1%	1.50 (0.68-2.95)	0.37
IVH grade III or IV	<1%	<1%	0.92 (0.37-1.88)	0.68
Necrotizing enterocolitis	<1%	1%	1.03 (0.38-2.29)	0.87

Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gafni A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

48

Those receiving multiple doses of corticosteroids also weighed less at birth than those exposed to placebo (2216 g vs 2330 g, p=0.0026), were shorter (44.5 cm vs 45.4 cm, p<0.001), and had a smaller head circumference (31.1 cm vs 31.7 cm, p<0.001)

	Antenatal corticosteroid (n=1164)	Placebo (n=1140)	Mean difference (95% CI)	P value
Birthweight (g)	2216 (28.3)	2330 (28.7)	−113.1 (37.3) (−187.0 to −41.17)	0.0026
Length at birth (cm)	44.5 (0.2)	45.4 (0.2)	−0.9 (0.25) (−1.34 to −0.37)	<0.001
Mean head circumference (cm)	31.1 (0.1)	31.7 (0.1)	−0.6 (0-.5) (−0.90 to −0.32)	<0.001
Intubation and ventilation via endotracheal tube	16%	19%	0.84 (0.63 to 1.09)	0.19
Neonatal infection	9%	8%	1.23 (0.88 to 1.67)	0.24

Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gelmi A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

49

Conclusion

Multiple courses of antenatal corticosteroids, every 14 days, do not improve preterm-birth outcomes and are associated with decreased weight, length, and head circumference at birth. Therefore, this treatment schedule is not recommended

Murphy KE, Hannah ME, Willan AR, Hewson SA, Ohlsson A, Kelly EN, Matthews SG, Saigal S, Asztalos E, Ross S, Delisle MF, Amankwah K, Guselle P, Gelmi A, Lee SK, Armson BA; Lancet. 2008 Dec 20;372(9656):2143-51

50

JAMA Network | Open

Original Investigation | Obstetrics and Gynecology

Timing of Antenatal Corticosteroid Administration and Neonatal Outcomes

Nir Melamed, MD, MSc; Kellie E. Murphy, MD; Christy Pylypjuk, MD; Rebecca Sherlock, MD; Guillaume Ethier, NNP; Eugene W. Yoon, MSc; Prakesh S. Shah, MD; for the Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators

Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

51

Methods

- Precise data on the optimal timing of administration are scarce
- To investigate the association between antenatal corticosteroids administration to the birth interval as a continuous variable and neonatal outcomes among preterm neonates

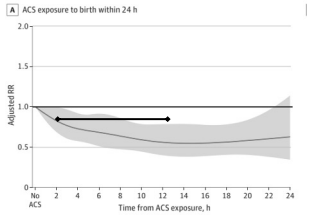
Methods

- A national retrospective cohort study
- Participants neonates born from 23 weeks 0 days to 31 weeks 6 days' gestation (n=7,950)
- Exposure: antenatal corticosteroid administration during the birth interval
- The primary outcome was neonatal mortality

Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

52

The reduction in risk of neonatal mortality associated with Antenatal corticosteroid use increased, reaching a plateau 12 hours following exposure

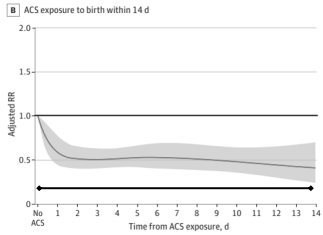


Relative risk 0.56 (95% CI: 0.40-0.78)

Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

53

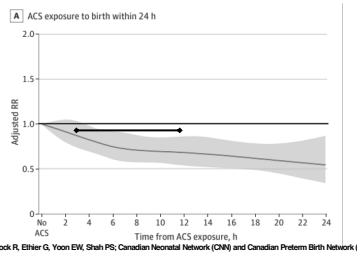
The reduction in the risk of neonatal mortality remained relatively stable for the first 2 weeks following exposure



Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

54

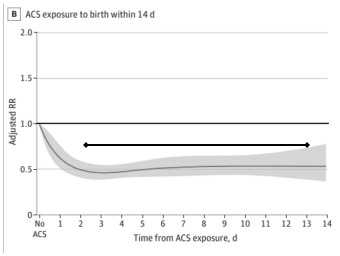
The reduction in risk of the composite outcome of Mortality or Severe Neurologic Injury associated with Antenatal corticosteroid use increased, reaching a plateau 12 hours following exposure



Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

55

The reduction in the risk of the composite outcome of Mortality or Severe Neurologic Injury remained relatively stable for the first 2 weeks following exposure



Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

56

Conclusions

Neonates born from 23 to 31+6 weeks of gestation, antenatal corticosteroid administration was associated with a reduction in neonatal mortality as early as 2 hours after the administration of the first dose. The interval associated with the greatest reduction in neonatal mortality was between 12 hours and 14 days before birth.

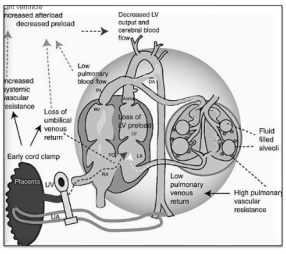
Melamed N, Murphy KE, Pylypjuk C, Sherlock R, Ethier G, Yoon EW, Shah PS; Canadian Neonatal Network (CNN) and Canadian Preterm Birth Network (CPTBN) Investigators. JAMA Netw Open. 2025 May 1;8(5):e2511315

57

Deferred Cord Clamping

58

Early cord clamping prior to the onset of lung aeration

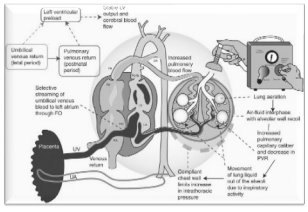


- **Immediate cord clamping prior to lung aeration restricts flow to the ventricles**
- **With failure to establish ventilation, pulmonary vascular resistance remains high and compromises pulmonary blood flow (increased right-to-left DA shunt) and venous return to the left ventricle**
- **Decreased filling of the left ventricle (preload) and increased afterload (due to removal of low-resistance placenta) compromise cardiac output**

Lakshminrusimha S, Van Meurs K. Pediatr Res. 2015 May;77(5):615-7

59

Physiologic (delayed) cord clamping after onset of lung aeration

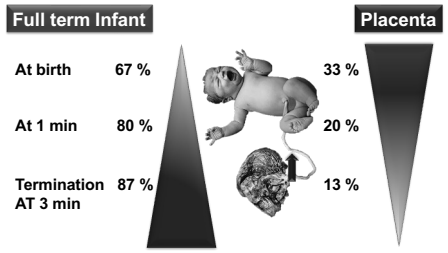


- **An intact umbilical cord allows continuous umbilical venous flow to the ventricles while respirations are being established**
- **With the concomitant initiation of breathing through crying or positive pressure ventilation, pulmonary vascular resistance decreases, allowing increased blood flow to the lungs (decreased right to left shunt through the ductus arteriosus as well as increased venous return to the LV)**
- **The unclamped UA prevents a sudden increase in left ventricular afterload.**
- **Result in stable cardiac output**
- **Clearance of lung liquid and an increase in resting air volume lead to thoracic expansion in the presence of a compliant chest wall, limiting the increase in intrathoracic pressure**

Lakshminrusimha S, Van Meurs K. Pediatr Res. 2015 May;77(5):615-7

60

Distribution of The Circulating Blood Volume in Delayed Cord Clamping



Yao AC, Moinian M, Lind J. Lancet. 1969 Oct 25;2(7626):871-3
https://www.scientificamerican.com/article/5-things-we-bet-you-didnt-know-about-the-placenta/

61

Deferred cord clamping, cord milking, and immediate cord clamping at preterm birth: a systematic review and individual participant data meta-analysis

Anna Lene Seidler, Mason Aberoumand, Kylie E Hunter, Angie Barba, Sol Libesman, Jonathan G Williams, Nipun Shrestha, Jannik Aagerup, James X Sotiropoulos, Alan A Montgomery, Gillian M L Gyte, Lelia Duley*, Lisa M Askie*, and iCOMP Collaborators†

Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

62

Methods

- To compare the effectiveness of deferred cord clamping, umbilical cord milking, and immediate cord clamping in reducing neonatal mortality and morbidity at preterm birth
- A systematic review and individual participant data meta-analysis
- Randomized controlled trials comparing deferred (also known as delayed) cord clamping, cord milking, and immediate cord clamping for preterm births (<37 weeks' gestation)
- The primary outcome was death before hospital discharge

Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

63

Results

- 2369 records, of which 48 randomised trials provided individual participant data and were eligible for our primary analysis
- We included individual participant data on 6367 infants

Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

64

Deferred cord clamping, compared with immediate cord clamping, reduced death before discharge by 32%

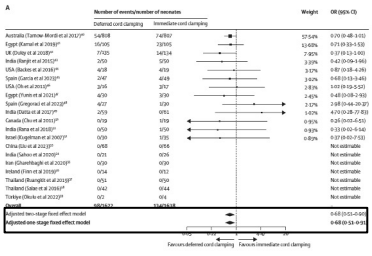
	Deferred cord clamping vs. immediate cord clamping	Cord miking vs. immediate cord clamping	Cord milking vs. deferred cord clamping
Primary outcome: mortality to discharge	0.68 (0.51-0.91)	0.73 (0.44-1.20)	0.95 (0.59-1.53)
Interventricular hemorrhage	0.98 (0.79-1.22)	1.02 (0.76-1.38)	1.04 (0.75-1.44)
Need for blood transfusion	0.59 (0.47-0.73)	0.69 (0.51-0.93)	1.07 (0.77-1.50)
Chronic lung disease	1.06 (0.87-1.3)	0.96 (0.63-1.47)	1.02 (0.56-1.87)
Hypothermia	1.28 (1.06-1.56)	0.95 (0.69-1.31)	0.90 (0.64-1.26)
Late onset sepsis	0.93 (0.73-1.19)	1.07 (0.76-1.51)	0.91 (0.57-1.48)
Necrotizing enterocolitis	0.82 (0.59-1.13)	0.90 (0.52-1.56)	0.95 (0.55-1.66)

- No clear evidence was found of a difference in death before discharge
  - Umbilical cord milking VS. immediate cord clamping
  - Umbilical cord milking VS. deferred cord clamping

Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

65

Deferred cord clamping, compared with immediate cord clamping, reduced death before discharge by 32%



Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

66

Conclusion

- High-certainty evidence that deferred cord clamping, compared with immediate cord clamping, reduces death before discharge in preterm infants
- This effect appears to be consistent across several participant-level and trial-level subgroups
- These results will inform international treatment recommendations

Seidler AL, Aberoumand M, Hunter KE, Barba A, Libesman S, Williams JG, Shrestha N, Aagerup J, Sotiropoulos JX, Montgomery AA, Gyte GML, Duley L, Askie LM; iCOMP CollaboratorsLancet. 2023 Dec 9;402(10418):2209-2222

67

The Beneficial Effects of Delayed Cord Clamping



Improves blood pressure | Improves Hct | Decreases IVH


Decreases NEC | Decreases RDS, BPD

Qian Y, Ying X, Wang P, Lu Z, Hua Y. Arch Gynecol Obstet. 2019 Sep;300(3):531-543

68

Preterm infants Delayed vs. Immediate Cord Clamping

Decrease Mortality
22 trials, 3083 participants
5.0% vs. 7.6%
OR 0.64 (0.39-0.99)

Decrease IVH
25 trials, 3316 participants
15.4% vs. 17.8%
OR 0.73 (0.54-0.97)

Decrease Blood transfusion
18 trials, 2904 participants
38.3% vs. 46.9%
OR 0.48 (0.32-0.66)

Jasani B, Torgalkar R, Ye XY, Syed S, Shah PS. Association of Umbilical Cord Management Strategies With Outcomes of Preterm Infants: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 2021 Apr 1;175(4):e210102
https://www.sscb.org/parent-care-in-neonatal-unit/care-in-nicu

69

Clinical Situations in which Immediate Umbilical Cord Clamping Should Be Considered

- The need for immediate resuscitation of the mother of the infant
- Fetal hydrops
- Disrupted utero-placental circulation (e.g., bleeding vasa previa)
- Know twin-to-twin transfusion syndrome or twin anemia polycythemia sequence

McDonald SD, et al. Joint SOGC-CPS Clinical Practice Guideline [published correction appears in *J Obstet Gynaecol Can.* 2022 Oct;44(10):1113]

70

"Placental transfusion achieved by delayed cord clamping is a relatively inexpensive and safe intervention that could provide significant benefits."

Oh, J Perinatol. 2011

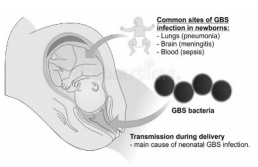
71

Antibiotics: GBS Prophylaxis

72

Antibiotics for GBS prophylaxis

- **Group B streptococcus GBS: Streptococcus agalactiae**
- **Colonize in GI and GU tract in 10-25% of pregnant women**
- **Associated with adverse pregnancy outcomes:**
  - **Preterm labor, PROM, Chorioamnionitis, and fetal infection**
  - **Maternal bacteriuria, pyelonephritis, osteomyelitis, postpartum mastitis, and puerperal infection**



Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

73

Antibiotics for GBS prophylaxis

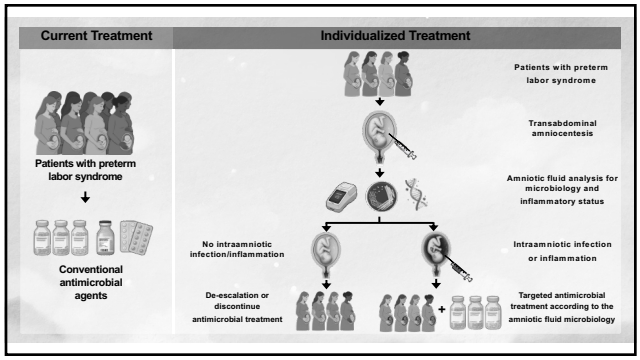
TABLE 67-2. Indications for Intrapartum Group B Streptococcal Infection Prophylaxis[a]

Intrapartum Prophylaxis Indicated	Intrapartum Prophylaxis Not Indicated
GBS bacteriuria	Negative vaginal–rectal culture obtained at ≥36 weeks' gestation during current pregnancy
Previous infant with invasive GBS disease	Cesarean delivery before labor onset or membrane rupture, regardless of GBS status or gestational age
Positive GBS screening culture during current pregnancy (unless cesarean delivery is performed before labor onset and with intact membranes)	Negative vaginal–rectal GBS culture in late gestation during the current pregnancy, regardless of intrapartum risk factors
Unknown GBS status at labor onset and any of the following: Birth at <37$^{0/7}$ weeks' gestation; Membrane rupture ≥18 hr; Intrapartum temperature ≥100.4° F (38.0°C); Intrapartum NAAT result positive for GBS; Positive GBS status in prior pregnancy	Unknown GBS status and intrapartum NAAT result negative and no intrapartum risk factors present

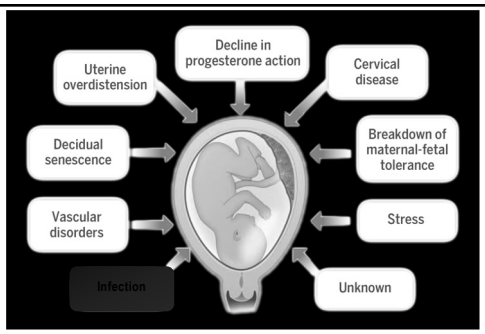
[a]Perform vaginal and rectal GBS culture at 36–38 weeks' gestation for all pregnant women, unless intrapartum antibiotic prophylaxis indicated for current pregnancy based on bacteriuria or prior infant with invasive GBS disease.
GBS = group B *Streptococcus*; NAAT = nucleic acid amplification test.

Williams Obstetrics. 26th ed. New York: McGraw-Hill; 2022.

74



75



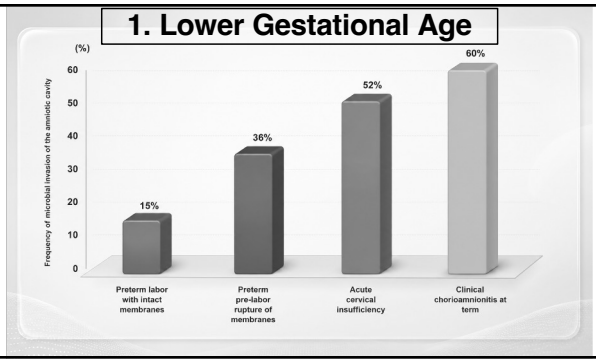
Romero R, Dey SK, Fisher SJ. Science. 2014;345:760-5.

76

Diagnosis – Amniocentesis

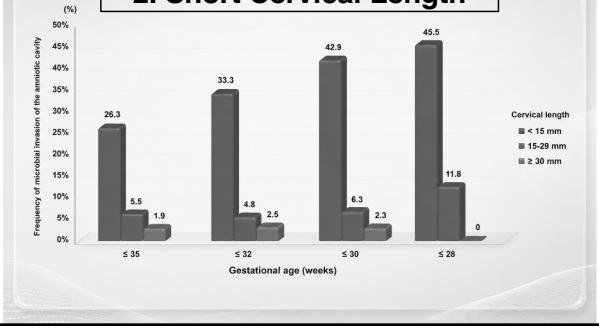
77

1. Lower Gestational Age



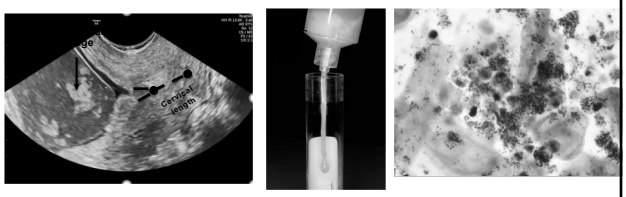
78

2. Short Cervical Length



79

3. Amniotic Fluid Sludge



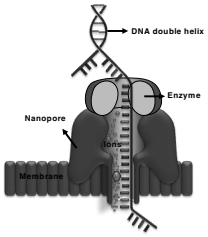
80

2025…

Rapid Diagnosis of Intra-amniotic Infection….

81

Third Generation: Nanopore Sequencing



- Long-read real time DNA sequencing
- Single molecule analysis
- Species level
- Polymicrobial organisms
- Rapid turn around time
- Portable device

https://www.yourgenome.org/facts/what-is-oxford-nanopore-technology-ont-sequencing/

82

Third Generation: Nanopore Sequencing

Courtesy of Dr. Piya Chaemsaithong

83

Preterm pre-labor rupture of membranes at 30 weeks Delivered by Cesarean

Culture of pus and uterine cavity: negative for bacteria

Courtesy of Dr. Piya Chaemsaithong

84

Nanopore sequencing results

15 min — Prevotella genus

2 hours — *Prevotella bivia* (species) at around 20x genome coverage

12 hours — *Prevotella bivia* contained cfxA3 (antimicrobial resistance gene)

Nanopore sequencing: rapid and accurate diagnosis of infection with anti-microbial resistance gene profiles

Chaemsaithong, P., Jenjaroenpun, P., Pongchaikul, P., Singsaneh, A., Thaipisuttikul, I., Romero, R., & Wongsurawat, T. (2023). Rapid detection of bacteria and antimicrobial resistant genes in intraamniotic infection using nanopore adaptive sampling. American journal of obstetrics and gynecology, 229(5), 590–593.e1.

85

Preterm Prediction and Prevention

86

Prediction

↓

Prevention

Roberto Romero, M.D., D. Med. Sci.

87

Methods to Predict Preterm Labor

History of preterm birth

Roberto Romero, M.D., D. Med. Sci.

88

History of Preterm Birth

- Increases the risk of a second preterm birth by approximately two-fold (25 – 37%)
- Only 15% of all preterm neonates are born to mothers with a prior history
- It is not helpful in nulliparous women

Roberto Romero, M.D., D. Med. Sci.

89

Transvaginal Ultrasound is the Gold Standard

All interventions tested in randomized clinical trials to prevent preterm birth In patients with a short cervix have been based on transvaginal ultrasound

Roberto Romero, M.D., D. Med. Sci.

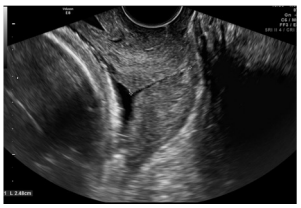
90

What is a "short cervix?"

Roberto Romero, M.D., D. Med. Sci.

91

Short Cervix ≤25mm

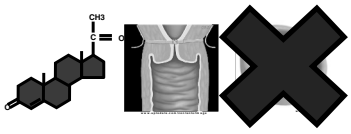


Less than 10th percentile

Roberto Romero, M.D., D. Med. Sci.

92

Prevention of Preterm Birth in Women with a Short Cervix (≤25 mm)

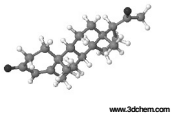


Progesterone | Cerclage | Pessary

Roberto Romero, M.D., D. Med. Sci.

93

Progesterone



www.3dchem.com

Essential for pregnancy maintenance

Roberto Romero, M.D., D. Med. Sci.

94

Reports of Major Impact ajog.org

Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data

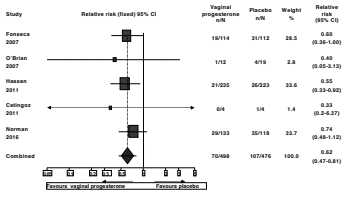
Roberto Romero, MD, DMedSci; Agustin Conde-Agudelo, MD, MPH, PhD; Eduardo Da Fonseca, MD; John M. O'Brien, MD; Elcin Cetingoz, MD; George W. Creasy, MD; Sonia S. Hassan, MD; Kypros H. Nicolaides, MD 2018

Individual Patient Data meta-analysis of vaginal progesterone in singleton gestation with a short cervix (<25 mm)?

Am J Obstet Gynecol 2018;218:161-180

95

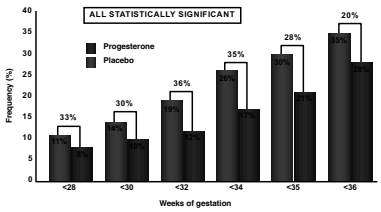
Vaginal progesterone reduceds the rate of preterm birth before 33 weeks' gestation



Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides K

96

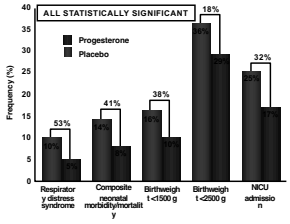
Effect of Vaginal Progesterone on Preterm Birth



Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides K. Am J Obstet Gynecol 2018; 218:161-80

97

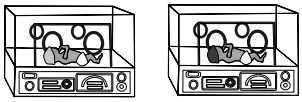
Effect of Vaginal Progesterone on Neonatal Outcome



Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides K. Am J Obstet Gynecol 2018; 218:161-80

98

Vaginal Progesterone Significantly Reduced:



	RR (95% CI)
1. Respiratory distress syndrome by 30%	0.70 (0.56-0.89)
2. Birthweight <1500 g by 47%	0.53 (0.35-0.80)
3. Mechanical ventilation by 46%	0.54 (0.36-0.81)
4. Neonatal death by 47%	0.53 (0.35-0.81)

99

Conclusion

Vaginal progesterone, but not 17OHPC, reduces the risk of preterm birth and improves perinatal outcome in women with a short cervix

Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides K

100

Comparison with other Interventions in Perinatal Medicine/Obstetrics

Intervention	To prevent:	RR (95% CI)	NNT (95% CI)
Magnesium sulfate	Eclampsia	0.41 (0.29-0.58)	100 (50-100)
Aspirin	Preeclampsia	0.83 (0.77.0.89)	72 (52-119)
Magnesium sulfate	Cerebral palsy	0.69 (0.55-0.88)	52 (31-154)
Antenatal corticosteroids	RDS	0.66 (0.59-0.73)	11 (9-14)
	Neonatal death	0.69 (0.58-0.81)	22 (16-36)
Vaginal progesterone in short cervix	Preterm birth <33 weeks	0.55 (0.33-0.92)	14 (8-87)
	RDS	0.39 (0.17-0.92)	22 (12-186)

NNT: Number Needed to Treat

101

SMFM Papers ajog.org

Cervical cerclage for singleton pregnant patients on vaginal progesterone with progressive cervical shortening

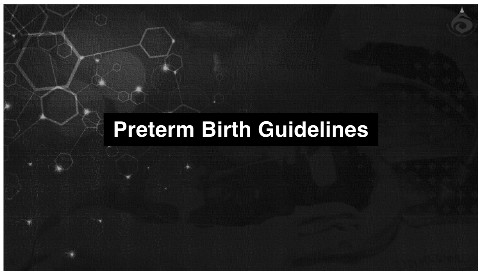
Check for updates

Christopher A. Enakpene, MD; Laura DiGiovanni, MD; Tiffany N. Jones, MD, MS; Megan Marshalla, BSc; Dimitrios Mastrogiannis, MD, MBA, PhD; Micaela Della Torre, MD, MS

Cervical Cerclage with vaginal progesterone significantly reduced spontaneous preterm birth and prolonged pregnancy latency when the cervical length becomes progressively shortened <10 mm while on vaginal progesterone

Enakpene CA, DiGiovanni L, Jones TN, Marshalla M, Mastrogiannis D, Della Torre M. Am J Obstet Gynecol. 2018;219:397.e1-397.e10. Roberto Romero, M.D., D. Med. Sci.

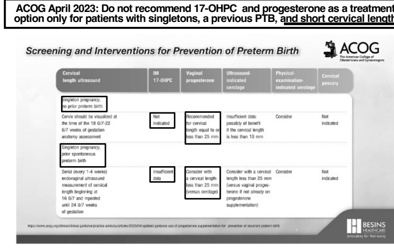
102



103

104

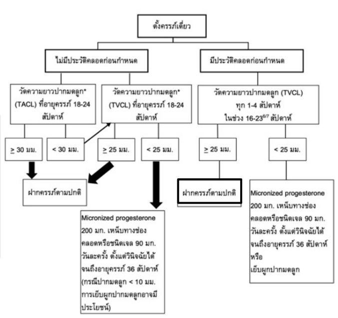
ACOG April 2023: Do not recommend 17-OHPC and progesterone as a treatment option only for patients with singletons, a previous PTB, and short cervical length



Cervical length ultrasound	IM 17-OHPC	Vaginal progesterone	Ultrasound-indicated cerclage	Physical-examination-indicated cerclage	Cervical pessary
Singleton pregnancy, no prior preterm birth					
Cervix should be visualized at the time of the 18 0/7-22 6/7 weeks of gestation anatomy assessment	Not indicated	Recommended for cervical length equal to or less than 25 mm	Insufficient data: possibly of benefit if the cervical length is less than 10 mm	Consider	Not indicated
Singleton pregnancy, prior spontaneous preterm birth					
Serial (every 1-4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation	Insufficient data	Consider with a cervical length less than 25 mm (versus cerclage)	Consider with a cervical length less than 25 mm (versus vaginal progesterone if not already on progesterone supplementation)	Consider	Not indicated

105

106



107

Conclusions

Management of preterm labor

- **Tocolysis**
- **MgSo4**
- **Cord clamping**
- **Antenatal corticosteroids**
- **GBS prophylaxis**

108

Conclusions

- A sononographic short cervix is a biomarker of sPTB
- Amniotic fluid sludge, early preterm
- Vaginal progesterone: short cervix, reduces sPTB and neonatal morbidity and mortality, cost-effectiveness
- Cervical cerclage
- No 17OHPC, No pessary

109

Thank you

110