Evidence based interventions to prevent spontaneous preterm birth

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No conflicts to declare

• I will discuss the off label use of vaginal progesterone

Objectives

- The national rate of preterm birth is about 11% with about ³/₄ of this being the result of spontaneous preterm birth.
- The indication for 17P is a history of spontaneous preterm birth in a singleton pregnancy now pregnant with a singleton gestation.
- The indication for vaginal progesterone is a shortened transvaginal cervical length
- The best indication for ultrasound-indicated cerclage is a history of spontaneous preterm birth <34 weeks and a transvaginal cervical length <25 mm
- Multiple gestations are at significantly increased risk of preterm birth and that the above interventions are not well demonstrated to be effective
- Pessary make be a new intervention to reduce spontaneous preterm birth

Long term trends PTB/LBW



Spontaneous v. Indicated



Goldenberg, Culhane, Iams, Romero, Lancet 2008

Indicated PTB

Timing of Indicated Late-Preterm and Early-Term Birth

Catherine Y. Spong, MD, Brian M. Mercer, MD, Mary D'Alton, MD, Sarah Kilpatrick, MD, PhD, Sean Blackwell, MD, and George Saade, MD



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



The Society for Maternal-Fetal Medicine

COMMITTEE OPINION

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The American College of Obstetricians and Gynecologists Committee on Obstetric Practice The Society for Maternal–Fetal Medicine

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Medically Indicated Late-Preterm and Early-Term Deliveries

References

 Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and earlyterm birth. Obstet Gynecol 2011;118:323-33. [PubMed] [Obstetrics & Gynecology] ♥

Condition	General Timing	Suggested Specific Timing
Placental/uterine issues		
Placenta previa*	Late preterm/early term	36 0/7–37 6/7 weeks of gestation
Placenta previa with suspected accreta, increta, or percreta*	Late preterm	34 0/7-35 6/7 weeks of gestation
Prior classical cesarean	Late preterm/early term	36 0/7-37 6/7 weeks of gestation
Prior myomectomy	Early term/term (individualize)	37 0/7-38 6/7 weeks of gestation
Fetal issues		
Growth restriction (singleton)		
Otherwise uncomplicated, no concurrent findings	Early term/term	38 0/7-39 6/7 weeks of gestation
Concurrent conditions (oligohydramnios, abnormal Doppler studies, maternal co-morbidity (eg, preeclampsia, chronic hypertension))	Late preterm/early term	34 0/7–37 6/7 weeks of gestation
Growth restriction (twins)		
Di-Di twins with isolated fetal growth restriction	Late preterm/early term	36 0/7-37 6/7 weeks of gestation
Di-Di twins with concurrent condition abnormal Doppler studies, maternal co-morbidity (eg, preeclampsia, chronic hypertension))	Late preterm	32 0/7-34 6/7 weeks of gestation
Mo-Di twins with isolated fetal growth restriction	Late preterm	32 0/7-34 6/7 weeks of gestation
Multiple gestations		
Di-Di twins	Early term	38 0/7-38 6/7 weeks of gestation
Mo-Di twins	Late preterm/early term	34 0/7-37 6/7 weeks of gestation
Oligohydramnios	Late preterm/early term	36 0/7-37 6/7 weeks of gestation
Maternal issues		
Chronic hypertension		
Controlled on no medications	Early term/term	38 0/7-39 6/7 weeks of gestation
Controlled on medications	Early term/term	37 0/7-39 6/7 weeks of gestation
Difficult to control	Late preterm/early term	36 0/7-37 6/7 weeks of gestation
Gestational hypertension	Early term	37 0/7-38 6/7 weeks of gestation
Preeclampsia—severe	Late preterm	At diagnosis after 34 0/7 weeks of gestation
Preeclampsia—mild	Early term	At diagnosis after 37 0/7 weeks of gestation
Diabetes		
Pregestational well-controlled*	Late preterm, early term birth not indicated	
Pregestational with vascular complications	Early term/term	37 0/7-39 6/7 weeks of gestation
Pregestational, poorly controlled	Late preterm or early term	Individualized
Gestational-well controlled on diet or medications	Late preterm, early term birth not indicated	
Gestational—poorly controlled	Late preterm or early term	Individualized
Obstetric issues		
PPROM	Late preferm	34 0/7 weeks of gestation

Etiology of Spontaneous PTB Spontaneous Preterm Parturition Syndrome

- Infection and inflammation
- Uteroplacental vascular disease and decidual hemorrhage
- Maternal and fetal stress
- Uterine overdistention
- Allergic phenomena
- Cervical disorders
- Hormonal disorders: suspension of progresterone action

Romero, Lockwood. *Pathogenesis of Spontaneous PTL*, Creasy & Resnik, 6th ed.

Progesterone

Preparations

Indications

- 17 hydroxyprogesterone caproate 250 mg IM weekly (17P)
- Micronized vaginal progesterone
 - Prometrium 200 mg qhs
 - Prochieve/Crinone 8% gel
 90 mg qhs

Prior SPTB

Short cervix

21st century seminal studies

- Meis, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. NEJM 2003.
- da Fonseca, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at risk: A randomized placebo-controlled double-blind study. AJOG 2003.

17 α-hydroxyprogesterone caproate



17P Historical studies

- Effective
 - Papiernik 1970
 - Johnson 1975
 - Yemini 1985
- No difference
 - Hartikainen-Sorri, 1980
 - Twins
 - Hauth 1983
 - Low risk (military)
- Keirse meta-analysis 1990

Meis 17P study

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 12, 2003

VOL. 348 NO. 24

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

 Paul J. Meis, M.D., Mark Klebanoff, M.D., Elizabeth Thom, Ph.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D., Atef H. Moawad, M.D., Catherine Y. Spong, M.D., John C. Hauth, M.D., Menachem Miodovnik, M.D.,
 Michael W. Varner, M.D., Kenneth J. Leveno, M.D., Steve N. Caritis, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D., Deborah Conway, M.D., Mary J. O'Sullivan, M.D., Marshall Carpenter, M.D., Brian Mercer, M.D., Susan M. Ramin, M.D., John M. Thorp, M.D., and Alan M. Peaceman, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

- Double blind, placebo controlled
- NICHD MFMU network, 19 centers
- 2:1 17P v. placebo (castor oil)
- Return after placebo

Meis 17P study

- Inclusion:
 - h/o SPTB (20+0 36+6; PTL or PPROM)
 - 15+0 20+3 wks
- Exclusion:
 - Multiples
 - Anomaly
 - P or heparin
 - HTN requiring meds
 - Seizure disorder
 - Cerclage

Meis 17P study

- Stopped early because exceeded threshold
- Decreased PTB <37, <35, <32 wks
- Improvement in some neonatal outcomes
- Higher than expected rates of PTB

Meis 17P outcomes

Table 2. Outcomes of Pregnancy According to Treatment Assignment.*					
Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)		
	no. (%	9			
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54-0.81)		
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)		
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)		
Black women	64 (35.4)	47 (52.2)	0.68 (0.51-0.90)		
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47-0.87)		
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48-0.93)		
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37-0.91)		

17P: When do we start?

- Meis/NICHD trial: 16+0 20+6
- How, Barton, Istwan, et al AJOG 2007
 <u>- 599 pts</u> 16+0 20+6

 $-333 \,\mu$ 5 10+0 - 20+0

- 307 pts 21+0 - 26+6

All patients	Early 17 P start at 16-20.9 weeks (n = 599)	Late 17 P start at 21-26.9 weeks (n = 307)	P value
Delivery $<$ 37 wk (%)	41.9	42.0	.973
${\sf SPTB}$ $<$ 37 wk (%)	32.7	35.8	.349
< 35 wk (%)	15.7	16.6	.721
< 32 wk (%)	5.8	4.2	.306

17P: When do we stop?

- Matria/Alere database (pts starting 16+0 20+6)
- 81 study pts
 - Stopped <32 wks
 - Undelivered >10 days
- 400 controls: 17P to 36+6

Research

www.AJOG.org

OBSTETRICS

Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate

Andrei Rebarber, MD; Lauren A. Ferrara, MD; Maryellen L. Hanley, MD; Niki B. Istwan, RN; Debbie J. Rhea, MPH; Gary J. Stanziano, MD; Daniel H. Saltzman, MD

Rebarber, et al

TABLE 3

Rates of recurrent spontaneous preterm delivery in patients with early cessation of 17P, compared with control

Variable	Control (n = 400)	Study (n $=$ 81)	P value
Gestational age at delivery (wk)*	36.4 ± 4.1	35.1 ± 4.2	<.001
Median gestational age at delivery (wk) [†]	37.4 (16.1, 43.3)	35.6 (19.4, 41.3)	
Spontaneous preterm delivery at $<$ 37 weeks of gestation (n)	133 (33.3%)	39 (48.1%)	.011
Spontaneous preterm delivery at $<$ 35 weeks of gestation (n)	56 (14.0%)	25 (30.9%)	<.001
Spontaneous preterm delivery at $<$ 32 weeks of gestation (n)	28 (7.0%)	13 (16.0%)	.020
* Data are presented as mean \pm SD.			

⁺ Data are presented as median (minimum, maximum).

The MUSC Story

- 2005: establishment of the March of Dimes Preterm Birth Prevention Clinic
 - Specialized clinic for women at risk for SPTB
 - Coincided with our using 17P
- Improved outcomes
 - Women with history of SPTB <33 wks, twice as likely to reach 36 weeks with 17P
 - Reduction in PTB <35 wks</p>
 - 2/3 reduction in regression analysis

THE NEW YORKER

ANNALS OF MEDICINE DECEMBER 6, 2004 ISSUE

THE BELL CURVE

What happens when patients find out how good their doctors really are?

BY ATUL GAWANDE

ORIGINAL ARTICLE

A Trial of 17 Alpha-Hydroxyprogesterone Caproate to Prevent Prematurity in Twins

Dwight J. Rouse, M.D., Steve N. Caritis, M.D., Alan M. Peaceman, M.D.,

- 661 pts
- Primary outcome, SPTB <35 wks
- Triplets, same story
- Need a higher dose?
- Pharmacokinetics



17P is not treatment for short cervix

Research

www.AJOG.org

OBSTETRICS WORLD PREMATURITY DAY

17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm

William A. Grobman, MD, MBA; Elizabeth A. Thom, PhD; Catherine Y. Sp Brian M. Mercer, MD; Alan T. N. Tita, MD; Dwight J. Rouse, MD; Yoram & Kenneth J. Leveno, MD; Sean Blackwell, MD; M. Sean Esplin, MD; Jorge E. John M. Thorp Jr, MD; Steve N. Caritis, MD; J. Peter Van Dorsten, MD; for *Kennedy Shriver* National Institute of Child Health and Human Developme Maternal-Fetal Medicine Units (MFMU) Network

- No difference in outcom
- Only 1/3 <20 mm
- <10% <15 mm



Grobman. 17 alpha-hydroxyprogesterone caproate for nulliparas with cervical length <30 mm. Am J Obstet Gynecol 2012.

Follow-up of Children Exposed In Utero to 17 α-Hydroxyprogesterone Caproate Compared With Placebo

Allison T. Northen, RN, BSN, Gwendolyn S. Norman, RN, BSN, MPH, Kristine Anderson, RN, BSN,

- Follow up of children in Meis study
- 2¹/₂-5 years old (mean 48 months)
- Development status
- Genital anomalies
- Gender identity
- FDA requested
- 348/463 still in MFMU
- 278/348 identified for f/u
- NO STATISTICAL DIFFERENCES

FDA-Approved Makena hydroxyprogesterone caproate injection Every week counts



\$\$\$\$\$\$\$\$\$

Micronized vaginal progesterone







Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study

Eduardo B. da Fonseca, MD, Roberto E. Bittar, PhD, MD, Mario H. B. Carvalho, MD, and Marcelo Zugaib, PhD, MD Sao Paulo, Brazil

- SPTB prevention
- 90% h/o SPTB
- Uterine anomaly, cervical insufficiency
- Decreased uterine activity

da Fonseca, NEJM, 2007

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Progesterone and the Risk of Preterm Birth among Women with a Short Cervix

Eduardo B. Fonseca, M.D., Ebru Celik, M.D., Mauro Parra, M.D., Mandeep Singh, M.D., and Kypros H. Nicolaides, M.D., for the Fetal Medicine Foundation Second Trimester Screening Group*

da Fonseca 2007



da Fonseca 2007

Table 2. Outcomes According to S	tudy Group.*				
Outcome	Progesterone Group† no. (9	Placebo Group <u>;</u> %)	Relative Risk (95% Cl)	P Value	
Maternal	()	-)			
Spontaneous delivery at <34 wk	24 (19.2)	43 (34.4)	0.56 (0.36–0.86)	0.007	
Any delivery at <34 wk	26 (20.8)	45 (36.0)	0.58 (0.38–0.87)	0.008	
			Cumulative Pregnancies	P=0.0	gesterone
			0 ¹ / ₁₆₀ / ₁₇₀	180 190 200 21	0 220
			No. at Risk for Spontaneous Birth	Gestational Age (day	»)
			Progesterone 125 125 Placebo 125 121	122 118 114 111 119 115 109 10	2 107 5 98

da Fonseca 2007

Maternal Characteristic	Total No. of Patients	No. Delivering Spontaneously at <34 Wk		P Value for Homogeneity
All patients	250	67	⊢ ●+	
Cervical length				0.25
<12 mm	125	44	⊢_ ●	
12–15 mm	125	23	► I	
Age				0.93
≥35 yr	46	18	F I	
<35 yr	204	49	⊢_ ● ¦	
Body-mass index				0.75
≥30.0	37	12	⊢	
20.0–29.9	187	49	⊢_ ●	
<20.0	26	6	• • • • • • • • • • • • • • • • • • •	
Race				0.65
White	95	33	⊢ _	
Black	137	28		
Other	18	6	• • • • • • • • • • • • • • • • • • •	
Obstetrical history				0.87
Parous with ≥1 previous preterm birth	38	16		
Parous with no previous preterm birth	72	13	⊢ ⊢	
Nulliparous	140	38	⊢ ●	
No. of gestations			1	0.69
Twin	24	11	·	
Singleton	226	56		
		0.01	0.1 1.0	10
			Progesterone Better Placebo	Better

Short cervix

• TVCL <= 15 mm 1.7%

-30.9% delivered preterm accounting for 25.8% of PTB

TVCL 16-25 mm in 8.3%
 -5.1% delivered preterm accounting for 20.4% of PTB

Progesterone vaginal gel

- 53 centers, 5 continents
- Singleton w/ h/o PTB 20-35 wks
- Procheive (Crinone) 8% vaginal gel (90 mg P) or placebo
- 611 pts
- No difference in outcomes (primary outcome SPTB <32 wks)
- Subset with TVCL <28 mm had improved SPTB <32 wks
 - Not <35, not <37
 - 19 pts P, 27 pts placebo

O'Brien, Adair, Lewis, et al, Ultrasound Obstet Gynecol, 2007 DeFranco, O'Brien, Adair, Lewis, et al, Ultrasound Obstet Gynecol, 2007

Hassan, 2011

- 32,091 women screened 20-23+6 (singletons only)
- 733 TVCL 10-20 mm
- 465 randomized to Prochieve gel or placebo
- Primary outcome, delivery < 33 weeks
- Treatment group 8.9%
- Placebo group 16.1%
- P=0.02 (95% CI 0.33-0.92)

Hassan, 2011

- Secondary outcomes
 - <28 wks 5.1% v. 10.3% p=0.04 (95% CI 0.25-0.97)
 - <35 wks 14.5% v. 23.3% p=0.02 (95% CI 0.42-0.92)
 - <37 wks 30.2% v. 34.1% p=0.38 (95% CI 0.68-1.16)

Romero, 2012

- Meta-analysis of vaginal progesterone studies
- Efficacy in singletons
- Trend in twins
- Decreased M&M in twins (23 treated, 29 placebo)

Cerclage and screening for cervical length

Transvaginal cervical length

- Normal distribution
- Shortens over pregnancy
- Little utility to measuring <16 weeks
- Excellent predictor of PTB risk
- Little variation by race/ethnicity or parity

TVCL values

- Mean/median 35-40 mm
- 25 mm ~10th percentile
- 15 mm ~2nd percentile
- 10 mm ~1st percentile
- Poor positive predictive value

Measuring TVCL



Easily learned

Ultrasound Obstet Gynecol 2002; 20: 575-579

Measuring cervical length with ultrasound: evaluation of the procedures and duration of a learning method

C. VAYSSIÈRE*, C. MORINIÈRE*, E. CAMUS*, Y. LE STRAT†, L. POTY*, J. FERMANIAN† and Y. VILLE*

*Department of Obstetrics and Gynaecology, University of Paris V, CHI Poissy, France, and †Department of Biostatistics, Hôpital Necker-Enfants malades, Paris, France

Cerclage

- History indicated
- Physical exam indicated
- Ultrasound indicated

Reserved for the previable pregnancy

History indicated cerclage

- Classically, recurrent 2nd trimester loss
- Generally reserved for the pt with >= 2-3 such deliveries
 - Place about 13 weeks, after aneuploidy screen
- Difficult to take an accurate history
- Confusion of changing evidence between time of loss and subsequent pregnancy

Physical exam indicated cerclage

- Dilation
- Visible membranes on speculum exam

Ultrasound indicated cerclage

Obstetrics & Gynecology, 2005

Cerclage for Short Cervix on Ultrasonography

Meta-Analysis of Trials Using Individual Patient-Level Data

Vincenzo Berghella, MD, Anthony O. Odibo, MD, Meekai S. To, MD, Orion A. Rust, MD, and Sietske M. Althuisius, MD



- Little improvement if no h/o SPTB
- Twins, RR for PTB <35 wks, 2.15 (1.15-4.01)
- Follow cervical length in pts with 1-2 SPTB

AJOG 2009

Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length

John Owen, MD; Gary Hankins, MD; Jay D. Iams, MD; Vincenzo Berghella, MD; Jeanne S. Sheffield, MD; Annette Perez-Delboy, MD; Robert S. Egerman, MD; Deborah A. Wing, MD; Mark Tomlinson, MD; Richard Silver, MD; Susan M. Ramin, MD; Edwin R. Guzman, MD; Michael Gordon, MD; Helen Y. How, MD; Eric J. Knudtson, MD; Jeff M. Szychowski, PhD; Suzanne Cliver, MSPH; John C. Hauth, MD



TABLE 2

Secondary perinatal outcomes for 301 women randomly assigned to cerclage or no-cerclage groups

Outcome	No cerclage (n = 153)	Cerclage (n = 148)	P value
Birth $<$ 7 d from randomization, n (%)	3 (2.0)	4 (2.7)	.72
Previable birth <24 wks, n (%)	21 (14)	9 (6.1)	.03
Preterm birth <37 wks, n (%)	91 (60)	66 (45)	.01
Perinatal death, n (%)ª	25 (16)	13 (8.8)	.046

^a One neonate in the cerclage group was lost to follow-up.

Owen. Cerclage for preterm birth prevention in shortened midtrimester cervical length. Am J Obstet Gynecol 2009.

Should we be screening everyone for cervical length

- Pro: Models say it is cost effective (about \$200 per pregnancy)
- Con: Mission creep, no actual trials showing cost effectiveness

- Low threshold for obtaining
- Obtain if unable to visualize CL >=25-35 mm transabdominally

Is Bedrest Helpful?

Activity Restriction Among Women With a Short Cervix

William A. Grobman, MD, MBA, Sharon A. Gilbert, MBA, PhD, Jay D. Iams, MD, Catherine Y. Spong, MD, George Saade, MD, Brian M. Mercer, MD, Alan T. N. Tita, MD, PhD, Dwight J. Rouse, MD, Yoram Sorokin, MD, Kenneth J. Leveno, MD, Jorge E. Tolosa, MD, MSCE, John M. Thorp, MD, Steve N. Caritis, MD, and J. Peter Van Dorsten, MD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network*

Is bedrest helpful?

•We don't know!

- Common sense
- Respond to symptoms
- Periodic rest

Other thoughts before conclusion

- Pessary
- Tocolytics—acute and maintenance
- Fetal fibronectin

 MOD toolkit <u>www.prematurityprevention.org</u>
- Celestone
 - Consider up to 36+6 esp for PPROM/PTL
 - Consider up to 38+6 for planned c/s

Summary

- 17P for singletons with a history of singleton SPTB
- Vaginal progesterone for a short cervix (<20 mm)
- U/S-indicated cerclage for singleton with TVCL <25 mm and h/o SPTB <34 weeks
- NO MEANINGFUL DATA COMBINING ANY 2 OF THESE INTERVENTIONS!!!
- Twins: little to offer except vaginal P
- Indicated PTB for maternal indications or to prevent stillbirth

Thanks!

