Evidence based interventions to prevent spontaneous preterm birth

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March 24, 2016
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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 ¾ 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
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>General Timing</th>
<th>Suggested Specific Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placental/uterine issues</strong></td>
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<tr>
<td>Placenta previa*</td>
<td>Late preterm/early term</td>
<td>36 0/7–37 6/7 weeks of gestation</td>
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<td>Placenta previa with suspected accreta, increta, or percreta*</td>
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<td>Prior myomectomy</td>
<td>Early term/term (individualize)</td>
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<td>38 0/7–39 6/7 weeks of gestation</td>
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<td>34 0/7–37 6/7 weeks of gestation</td>
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<td>Di–Di twins with concurrent condition</td>
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<td>abnormal Doppler studies, maternal co-morbidity [eg, preeclampsia, chronic hypertension]</td>
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<td>Mo–Di twins with isolated fetal growth restriction</td>
<td>Late preterm</td>
<td>32 0/7–34 6/7 weeks of gestation</td>
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<td>37 0/7–39 6/7 weeks of gestation</td>
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<td>Gestational hypertension</td>
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<td>Preeclampsia—severe</td>
<td>Late preterm</td>
<td>At diagnosis after 34 0/7 weeks of gestation</td>
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<td>Preeclampsia—mild</td>
<td>Early term</td>
<td>At diagnosis after 37 0/7 weeks of gestation</td>
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<td><strong>Diabetes</strong></td>
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<td>Pregestational well-controlled*</td>
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<td>Pregestational with vascular complications</td>
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<td>37 0/7–39 6/7 weeks of gestation</td>
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<td>Late preterm or early term</td>
<td>Individualized</td>
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<td>Gestational—well controlled on diet or medications</td>
<td>Late preterm, early term birth not indicated</td>
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<tr>
<td>Gestational—poorly controlled</td>
<td>Late preterm or early term</td>
<td>Individualized</td>
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<td><strong>Obstetric issues</strong></td>
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<tr>
<td>PPROM</td>
<td>Late preterm</td>
<td>34 0/7 weeks of gestation</td>
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</tbody>
</table>
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 progesterone action

Progesterone

Preparations

• 17 hydroxyprogesterone caproate 250 mg IM weekly (17P)

• Micronized vaginal progesterone
  – Prometrium 200 mg qhs
  – Prochieve/Crinone 8% gel 90 mg qhs

Indications

• Prior SPTB

• Short cervix
21st century seminal studies


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

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
### Table 2. Outcomes of Pregnancy According to Treatment Assignment.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone Group (N=306)</th>
<th>Placebo Group (N=153)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery before 37 wk of gestation</td>
<td>111 (36.3)</td>
<td>84 (54.9)</td>
<td>0.66 (0.54–0.81)</td>
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<tr>
<td>Spontaneous</td>
<td>90 (29.4)</td>
<td>69 (45.1)</td>
<td>0.65 (0.51–0.83)</td>
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<tr>
<td>Indicated because of complications</td>
<td>21 (6.9)</td>
<td>15 (9.8)</td>
<td>0.70 (0.37–1.32)</td>
</tr>
<tr>
<td>Black women</td>
<td>64 (35.4)</td>
<td>47 (52.2)</td>
<td>0.68 (0.51–0.90)</td>
</tr>
<tr>
<td>Nonblack women</td>
<td>47 (37.6)</td>
<td>37 (58.7)</td>
<td>0.64 (0.47–0.87)</td>
</tr>
<tr>
<td>Delivery before 35 wk of gestation</td>
<td>63 (20.6)</td>
<td>47 (30.7)</td>
<td>0.67 (0.48–0.93)</td>
</tr>
<tr>
<td>Delivery before 32 wk of gestation</td>
<td>35 (11.4)</td>
<td>30 (19.6)</td>
<td>0.58 (0.37–0.91)</td>
</tr>
</tbody>
</table>
17P: When do we start?

- Meis/NICHD trial: 16+0 – 20+6
  - 599 pts 16+0 – 20+6
  - 307 pts 21+0 – 26+6

<table>
<thead>
<tr>
<th>All patients</th>
<th>Early 17 P start at 16-20.9 weeks (n = 599)</th>
<th>Late 17 P start at 21-26.9 weeks (n = 307)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery &lt; 37 wk (%)</td>
<td>41.9</td>
<td>42.0</td>
<td>.973</td>
</tr>
<tr>
<td>SPTB &lt; 37 wk (%)</td>
<td>32.7</td>
<td>35.8</td>
<td>.349</td>
</tr>
<tr>
<td>&lt; 35 wk (%)</td>
<td>15.7</td>
<td>16.6</td>
<td>.721</td>
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<tr>
<td>&lt; 32 wk (%)</td>
<td>5.8</td>
<td>4.2</td>
<td>.306</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 400)</th>
<th>Study (n = 81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at delivery (wk)*</td>
<td>36.4 ± 4.1</td>
<td>35.1 ± 4.2</td>
<td>&lt;.001</td>
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<tr>
<td>Median gestational age at delivery (wk)†</td>
<td>37.4 (16.1, 43.3)</td>
<td>35.6 (19.4, 41.3)</td>
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<tr>
<td>Spontaneous preterm delivery at &lt;37 weeks of gestation (n)</td>
<td>133 (33.3%)</td>
<td>39 (48.1%)</td>
<td>.011</td>
</tr>
<tr>
<td>Spontaneous preterm delivery at &lt;35 weeks of gestation (n)</td>
<td>56 (14.0%)</td>
<td>25 (30.9%)</td>
<td>&lt;.001</td>
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<tr>
<td>Spontaneous preterm delivery at &lt;32 weeks of gestation (n)</td>
<td>28 (7.0%)</td>
<td>13 (16.0%)</td>
<td>.020</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± 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
  – 2/3 reduction in regression analysis
THE BELL CURVE

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

BY ATUL GAWANDE
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

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

- No difference in outcomes
- Only 1/3 <20 mm
- <10% <15 mm
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
- 2½-5 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
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*
24,620 Pregnant women underwent measurement of cervical length

413 Had a cervical length of 15 mm or less

250 Agreed to participate and underwent randomization

125 Received progesterone and all were followed up
116 Had adherence of 80% or more

125 Received placebo and all were followed up
118 Had adherence of 80% or more

da Fonseca 2007
Table 2. Outcomes According to Study Group.†

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progesterone Group†</th>
<th>Placebo Group‡</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Maternal</td>
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<tr>
<td>Spontaneous delivery at &lt;34 wk</td>
<td>24 (19.2)</td>
<td>43 (34.4)</td>
<td>0.56 (0.36–0.86)</td>
<td>0.007</td>
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<td>Any delivery at &lt;34 wk</td>
<td>26 (20.8)</td>
<td>45 (36.0)</td>
<td>0.58 (0.38–0.87)</td>
<td>0.008</td>
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† specifics not provided
‡ specifics not provided
<table>
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<tr>
<th>Maternal Characteristic</th>
<th>Total No. of Patients</th>
<th>No. Delivering Spontaneously at &lt;34 Wk</th>
<th>P Value for Homogeneity</th>
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<tr>
<td>All patients</td>
<td>250</td>
<td>67</td>
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<td>Cervical length</td>
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<td>&lt;12 mm</td>
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<td>12–15 mm</td>
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<td>Age</td>
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<td>≥35 yr</td>
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<td>≥30.0</td>
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<td>20.0–29.9</td>
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<td>Nulliparous</td>
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<td>Twin</td>
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<tr>
<td>Singleton</td>
<td>226</td>
<td>56</td>
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</table>
Short cervix

- TVCL $\leq 15$ 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

Hassan, 2011

- 32,091 women screened 20-23+6 (singleton 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 \(~10\text{th}\) percentile
- 15 mm \(~2\text{nd}\) percentile
- 10 mm \(~1\text{st}\) percentile
- Poor positive predictive value
Measuring TVCL
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 2\textsuperscript{nd} trimester loss
• Generally reserved for the pt with \( \geq 2-3 \) 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

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
Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened mid trimester 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No cerclage (n = 153)</th>
<th>Cerclage (n = 148)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth &lt;7 d from randomization, n (%)</td>
<td>3 (2.0)</td>
<td>4 (2.7)</td>
<td>.72</td>
</tr>
<tr>
<td>Preivable birth &lt;24 wks, n (%)</td>
<td>21 (14)</td>
<td>9 (6.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Preterm birth &lt;37 wks, n (%)</td>
<td>91 (60)</td>
<td>86 (57)</td>
<td>.01</td>
</tr>
<tr>
<td>Perinatal death, n (%)</td>
<td>25 (16)</td>
<td>13 (8.8)</td>
<td>.046</td>
</tr>
</tbody>
</table>

*One patient in the cerclage group was lost to follow-up.

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

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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 [www.prematurityprevention.org](http://www.prematurityprevention.org)
- 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!