PREVENTION OF PRETERM BIRTH

Progesterone Supplementation

Roger L. Wallace, D.O. | September 17, 2020
Agenda

• Welcome
  • This meeting is for education purposes
  • The presentation will be recorded and archived for future reference

• Questions for discussion
  • Please enter in CHAT for discussion at the end of the presentation

• CE / CME
  • Need to complete a short survey; you will receive an email in 1-2 wks following the presentation

• Meeting Logistics
  • Please mute microphone
CORE is a network designed to create a diverse medical community, connecting prenatal providers and professionals in Montana and Wyoming. This supportive network of peers and specialists who are committed to reduce preterm birth rates and improve the health and survival of both mom and baby.
Maternal health complications, racial disparities, and social determinants of health, affect the health and survival of both mom and baby.

**Montana**

- **9.1% Preterm Birth Rate**
- Prematurity Grade: **B-**

Preterm birth rate among American Indian women is 60% higher than all other women.

**Wyoming**

- **9.8% Preterm Birth Rate**
- Prematurity Grade: **C**

*2019 March of Dimes Preterm Birth Report Card*
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Disclosure

I have no actual or potential conflict of interest in relation to this program / presentation.
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Incidence/Implications (<37 weeks)

- One of the most common complications of pregnancy. 11.1% world-wide; 10% U.S.
  - Black infants (13.8%); American Indian/Alaska Natives (11.6%); Hispanics (9.6%); Whites (9.1%); Asian/Pacific Islanders (8.7%)
  - Multiples 8X more likely to be preterm compared to singletons
  - Associated infant mortality 5.8/1000 total US live births (8.6 for mat age < 20 y/o; 6.2 20-29 y/o; 5.0, 30-39 y/o; 7.3 > 40 y/o)
  - Associated morbidities; RDS, BPD, sepsis, IVH, NEC, ROP, Long-term CP and development disability
  - 2005 Annual cost of care (first year of life): 26.2 billion > cost of care at term; 2/3 = medical care
  - Only CP, MR, VI, HL included in calculations; cost of caregivers can be > medical care $; data on education $ not available.
  - Extremely preterm (< 28 wks) = 6% all PTB, account for > 1/3 of total $ through 7 yrs of age
  - Very preterm (28-31 wks), Moderately/Late preterm (32-36 wks) = large majority of cases
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Risk Factors

- Hx of PTB, short CL (<25mm), AMA, multiples, infectious diseases, smoking, uterine anomaly, Hx of D&C/conization
- Hx of PTB and short CL (<25mm) = most predictive factors. 1 prior PTB = 15-20% RR, 2 prior PTB = 30-50% RR; also increased with < EGA in prior pregnancy
- Recent review and meta-analysis showed pts w previous preterm TWIN births, at increased odds of preterm birth is subsequent singleton pregnancies (OR = 4.34)
- EGA at previous twin preterm birth: 34-37wks = OR 2.13; 30-34wks = OR 5.18; < 30wks = OR 9.78
- The most effective treatment of PTB = Prediction and Prevention of risks
- Dx and Rx of asymptomatic bacteriuria and smoking cessation = most common preventable cause(s)
- The most common/representative method of PTB prevention in pts. w Hx PTB or short CL
- PROGESTERONE SUPPLEMEN TATION THERAPY.
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Progesterone Supplementation Rx

• Within the 7 years of exclusivity under the Orphan Drug Act, Makena was the sole FDA-approved source of 17p for PTB prevention, until 2018 when generic formulations were approved by the FDA
• 3 subsequent R/PC trials comparing 17P and vaginal progesterone show no evidence of a difference in effect on PTB and PNM (small sample sizes/concerns re generalizability). Nonrandomized studies in US found no benefit for 17P in preventing recurrent PTB
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Progesterone Supplementation Rx

• The FDA AAP requires subsequent studies using clinical outcomes to evaluate benefit. EGA at delivery was eventually rejected the EGA surrogate outcome as a substitute for clinical benefit, but eventually recognized EGA at delivery as an acceptable endpoint and granted the accelerated approval of Makena in Feb, 2011.
• Makena convinced FDA that the confirmatory trial (PROLONG, a multicenter international randomized placebo controlled trial, with at least 10% from US sites) was feasible and could be completed by 2017
• During this time (PROLONG on-going/delayed), Makena achieved significant financial gain, and when AMAG Pharmaceuticals purchased in 2014, they proceeded to make more than $1.2 billion in revenue until 2018 when generic competition entered the market.
• PROLONG enrolled 1708 women/9 countries, 391 in US. 23.1% of pts on Makena delivered < 37 weeks vs 21.9% in placebo group.
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FDA Advisory Committee Hearing: Center for Evidence-based Policy at Oregon Health & Science University, Portland, Oregon. 2018.

- Automatically triggered after confirmatory trials for drugs granted accelerated approval by FDA
- Committee vote results:
  - 16-0 - PROLONG did not provide required evidence of clinical benefit; 13-3 – the 2 prominent trials w large samples in the U.S. did not support clinical benefit of Makena for neonatal outcomes; 9-7 recommend FDA withdraw approval of Makena for prevention of recurrent PTB.
  - ACOG, SMFM still encourage use of 17P until planned meta-analysis and secondary analysis of data available and for pts who have characteristics similar to the initial Meis, et al population (pts at high risk for PTB)
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Progesterone Supplementation

- 2 types commonly used in randomized trials: 17P and natural micronized progesterone
- 17p IM injection once weekly
- Natural micronized progesterone
  - Vaginal suppository 100, 200, 400 mg Daily
  - Vaginal gel 90 mg Daily
  - Oral capsule 200, 400 mg Daily

- administered orally metabolized in liver, loses potency, irregular blood levels, increased side effects. Administered vaginally avoids first-pass liver effect, absorbed quickly, increased bioavailability, directly affects the uterus, maintains high concentration in serum
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Treatment Options

• 17-alpha hydroxyprogesterone caproate (17P)
  • Despite the findings of the PROLONG study, ACOG and SMFM encourage use and state it is reasonable to prescribe 17P to patients who have characteristics similar to the Meis et al population, i.e. higher risk for PTB

• Vaginal progesterone
  • 2003 da Fonseca et al: R, DB, PC study in high-risk patients with > 90% w Hx PTB. Daily 100 mg micronized progesterone vaginal suppository daily = significantly lower rates of PTB <37 and <35 weeks. 3 subsequent randomized trials supported these findings.
  • O’Brien et al (Obstet Gynecol), 2007;30 showed Rx with 90 mg vaginal natural micronized progesterone gel resulted in significant lower rates of PTB < 32 wks, lower NICU admissions, shorter hospital stay in patients with a Hx of PTB and CL, 28mm
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Vaginal progesterone
- A recent (AJOG, Feb, 2018) meta-analysis of vaginal progesterone for singleton gestations with short cervix in preventing PTB showed a significant reduction in PTB <33 wks (RR = 0.62) as well as similar significant reductions in PTB <36 – 34 wks, 32, 30 and 28 wks, with significant reductions in RDS, composite NNM/M, Bwt < 1500 and 2500 gms. There were 7 (1.4%) NND in progesterone group and 15 (3.2%) in the placebo group.
- Similar results have been shown with daily micronized progesterone gel (90mg/day) in randomized studies as well as meta-analysis with significantly reduced rates of PTB <28, <32, and <35 weeks, in addition to lower rates of RDS, NNM, VLBW infants, NICU admissions and mechanical ventilator use.

Twin pregnancies 17P
- ACOG and SMFM have concluded that progesterone supplementation in multiple pregnancies lacks sufficient evidence of significantly reducing the risk of PTB. A R, DB, PC study by NICHD, MFMUN in 2017 (NEJM 2007, 357) found that 17P did not reduce the rate of PTB in twin pregnancies with a CL < 25mm, even at a higher dose of 500mg twice weekly. And the rate of PTB < 32 wks was higher in the 17P group than the control group.
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Twin pregnancy vaginal progesterone

- A randomized trial (Arch Gynecol Obstet 2016: 293) pts with twin pregnancy and CL < 25mm, 400mg micronized progesterone vaginal suppository Rx was associated with lower rates of PTB >34 and < 32 wks, longer GAD, decreased rates of VLBW infants, RDS, NNM and use of mechanical ventilators.

- An updated meta-analysis of individual patient data (Ultrasound Obstet Gynecol 2017;49) comparing vaginal progesterone w placebo/no Rx in pts with twins and short CL resulted in significant decrease in rates of PTB <35-30 wks and NNM/M. They also demonstrated significantly lower rates of PTB >34 and 32 wks, lower rate of adverse drug reactions, and lower rate of NICU admissions for pts receiving vaginal progesterone vs 17P.

- A recent (AJOG June 2019; 543) systematic review and meta-analysis indicates that cerclage placement provides significant benefit in reducing PTB and significantly prolongs pregnancy in twin pregnancies with a CL <15mm, or dilated cervix of >10mm.

PROM/PTL

- Neither 17P, nor vaginal progesterone have been shown to significantly decrease rate(s) of PTB, increase GAD, or improve neonatal outcomes.
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SUMMARY

• Many studies and guidelines from societies and associations validate progesterone supplement Rx effectively preventing PTB in pts with Hx of PTB and in pts with short CL
• It has not been fully proven which progesterone Rx is superior regarding efficacy of preventing PTB, cost-effectiveness, or side effects.
• There is a definite trend towards demonstration of overall beneficial effects of vaginal progesterone if reducing PTB and NNM/M. The original Meis data and subsequent comparative studies suggest that 17P MIGHT BE most beneficial in preventing PTB < 32 weeks.
• Both micronized progesterone (vaginal suppositories and gel) and 17P are available in generic form.
## Tools & Resources

### INDICATIONS for progesterone supplementation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singleton pregnancy, prior spontaneous singleton preterm birth; normal cervical length:</td>
<td>YES</td>
</tr>
<tr>
<td>Singleton pregnancy, prior spontaneous twin preterm birth; normal cervical length:</td>
<td>POSSIBLY</td>
</tr>
<tr>
<td>Singleton pregnancy, no prior spontaneous preterm birth; short cervix (≤20 mm):</td>
<td>YES</td>
</tr>
<tr>
<td>Multiple pregnancy (twins or triplets) without prior preterm birth; normal cervical length:</td>
<td>POSSIBLY</td>
</tr>
<tr>
<td>Twins, prior preterm birth:</td>
<td>POSSIBLY</td>
</tr>
<tr>
<td>Twins, short cervix:</td>
<td>NO</td>
</tr>
<tr>
<td>Preterm premature rupture of membranes:</td>
<td>NO</td>
</tr>
<tr>
<td>Positive fetal fibronectin test:</td>
<td>NO</td>
</tr>
<tr>
<td>Undelivered after an episode of preterm labor:</td>
<td>UNCLEAR</td>
</tr>
</tbody>
</table>
Current singleton pregnancy with a **Prior Spontaneous Preterm Birth**

Prior singleton live birth 16<sup>0</sup>-36<sup>6</sup> weeks gestation due to labor, ruptured membranes, cervical dilation / insufficiency, abruption*

Recommend 250 mg IM weekly 17-alpha hydroxyprogesterone caproate (initiate at 16 weeks, through 36 weeks)

- **Serial Transvaginal Ultrasound for CL***
  - (first at 16 weeks; until 23 / 26/7 weeks)

  - **CL ≥ 30 mm**
    - **< 24 weeks**
      - Yes: Routine prenatal care, continue 17P
      - No: 2 weeks
    - **≥ 24 weeks**
      - Yes: Routine prenatal care, continue 17P
      - No: 1 week

  - **CL 26-29 mm**
    - **< 24 weeks**
      - Yes: Routine prenatal care, continue 17P
      - No: 1 week
  - **CL ≤ 25 mm**
    - Sterile speculum examination, Evaluate for labor, intraamniotic infection, etc.
    - Offer ultrasound indicated cerclage, continue 17P

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* Women with a history of abruption related to preterm labor and ppr, or unrelated to other obvious causes (e.g., IV drug use, polyhydramnios) may be candidates for 17P. Careful review of historical factors and review of prior delivery records is imperative.
** For most women with CL ≥ 30 mm, q2 week ultrasound evaluation is appropriate.
*** Should be performed by credentialed sonographer or credentialed physician and interpreted by trained/credentialed physician.
Current singleton pregnancy with a
No prior Spontaneous Preterm Birth

**Address Barriers:**
- Adequate review of all risk factors by provider (adequate time, IPI, etc.)

→ Review ALL PTB Risk Factors*

→ Screen for: Urine Culture; RPR/GC/Chlam

→ Consider Single Transvaginal CL Ultrasound (at 18-23 weeks of gestation)

→ CL ≤20 mm
  - Vaginal Progesterone**

→ CL >20 mm
  - No intervention

→ If pos., see appropriate guideline (smoking, etc.)

**Address Barriers:**
- Provider knowledge re: importance of TVU, interpretation of images (CLEAR for Quality)
- Access to TVS by trained clinicians

*See Table of Risk Factors in text
** 90mg gel, or 200mg suppositories, q day until 36 weeks of gestation

No cerclage, or pessary, for these women
Tools & Resources

SMFM Preterm Birth Toolkit app

SMFM Preterm Birth Toolkit Webpage
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There is a difference between knowledge and wisdom. Knowledge is knowing that a tomato is a fruit, wisdom is not including in a fruit salad.

The secret to discovery is not in seeking new landscapes, but seeing the current landscape with new eyes.
Questions?

Thank you for your time and attention
NEXT TeleCORE Session

October 15, 2020

Implicit Bias

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For more information about CORE and to register for upcoming sessions, please visit sclhealth.org/CORE.

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