PROGESTERONE AND THE PREVENTION OF PRETERM BIRTH: THE SAGA CONTINUES

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Errol R. Norwitz, M.D., Ph.D. has no conflicts of interests to disclose.
Objectives

- Discuss the various strategies to prevent preterm birth
- Understand the rationale behind progesterone supplementation to prevent recurrent preterm birth
- Define subgroups of women who will benefit from progesterone supplementation
We are getting better at identifying women at risk for PTB

... but have had only limited success in preventing it
Tertiary prevention

- **Tocolytic therapy**
  - Magnesium sulfate
  - β-mimetic agonists
  - Calcium channel blockers
  - NSAID
  - Oxytocin receptor blockers

- Does **not** significantly reduce the risk of PTB or perinatal morbidity
Secondary prevention

- **Improved identification of patients at high-risk of PTB**
  - Cervicovaginal fetal fibronectin (fFN)
  - Transvaginal cervical length measurements
  - Risk factor scoring

- **Implementation of strategies to prevent PTB in high-risk patients**
Effective strategies for the prevention of PTB

- Prevention of multifetal pregnancies
- Cervical cerclage, if indicated
- Prevention, early diagnosis, and effective treatment of genitourinary infections and STIs
- Stop smoking and substance abuse
Preventive strategies without proven benefit

- Intensive prenatal care
- Bed rest, flexible workforce policies
- Screening and treating asymptomatic women for STIs / gingival disease
- Broad-spectrum antibiotic therapy
- Maintenance tocolysis
Primary prevention
Pre- and peri-conceptional origins of PTB

Control sheep
Sheep starved around conception so that they lose 15% of their body weight

Pre- and peri-conceptional origins of PTB

Low PAPP-A (not $\beta$-hCG) at 8-12 weeks is associated with low birth weight and PTB

Pre- and peri-conceptional origins of PTB

Small fetal size in the first trimester (expressed as difference between observed and expected CRL) is associated with low birth weight and PTB

Table 2: Associations between observed minus expected size of fetus in first trimester (AGA) and birth weight, duration of pregnancy, and delivery of small for gestational age infant (FASTER trial; n=976)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted</th>
<th>Adjusted for maternal characteristics*</th>
<th>Adjusted for maternal characteristics* and pregnancy complications†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient/odds ratio‡ (95% CI)</td>
<td>P value</td>
<td>Coefficient/odds ratio‡ (95% CI)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>28.2 (14.9 to 41.2)</td>
<td>&lt;0.0001</td>
<td>27.9 (14.6 to 41.2)</td>
</tr>
<tr>
<td>Duration of pregnancy (days)</td>
<td>0.42 (0.10 to 0.73)</td>
<td>0.009</td>
<td>0.48 (0.17 to 0.80)</td>
</tr>
<tr>
<td>Delivery of SGA infant</td>
<td>0.87 (0.81 to 0.94)</td>
<td>&lt;0.0001</td>
<td>0.88 (0.82 to 0.96)</td>
</tr>
</tbody>
</table>

Multiple micronutrient supplementation is associated with fewer low birth weight / SGA babies c/w placebo. Insufficient data on PTB, preeclampsia, pPROM, abruption.

Haider BA, Bhutta ZA. Cochrane Database Syst Rev 2006; 4:CD004905 (meta-analysis of 9 trials including 15,378 women)
Preconceptional folate supplementation for ≥1 year is associated with decreased perinatal mortality (RR 0.63, 95% CI, 0.42-0.95; p=0.027)

(secondary analysis of FASTER Trial; folate dose / duration correlated with spontaneous PTB and perinatal outcome in 34,480 singleton pregnancies)
What about progesterone to prevent preterm birth?

PRO-GE

GESTATIONAL

STEROIDAL

KETONE
Progesterone in pregnancy

- Adequate production of progesterone by corpus luteum of ovary is critical for the success of early pregnancy
  - Surgical removal of corpus luteum leads to abortion
  - Progesterone receptor antagonists (RU 486) given <7 weeks (49 days) leads to loss of pregnancy

- Role of progesterone in the latter half of pregnancy is not clear
What do these three species have in common?
“The observation that levels of progesterone in the maternal circulation do not change in the week prior to labor does not preclude the possibility that labor may require a localized withdrawal of progesterone at the level of the uterus”

Professor Sir Alexander Turnbull, 1988
Nuffield Dept. of Obstetrics & Gynecology
The John Radcliffe Hospital, Oxford, U.K.
Progesterone to prevent PTB: What does the data show?

In 1970-1990s, several clinical trials found that prophylactic administration of progesterone was associated with a 15-70% ↓ in preterm birth, but no ↓ in perinatal mortality / morbidity.

Keirse MJNC. *Br J Obstet Gynaecol* 1990; 97:149-54
What happened in 2003?

In 2003, two placebo-controlled RCTs on use of progesterone supplementation to prevent recurrent PTB in high-risk women

(n=459, 17P 250-mg IMI weekly 16-20 through 36 weeks)
(n=142, vaginal supp 100-mg daily 24 through 34 weeks)
Progestosterone and PTB

Progestosterone supplementation can prevent PTB in some high-risk women

- **Prior spontaneous PTB**
  (RCT, n=459, 17P 250-mg IMI weekly 16-20 through 36 weeks)
  (RCT, n=142, vaginal supp 100-mg daily 24 through 34 weeks)

- **Cervical shortening**
  (RCT, n=413, CL <1.5 cm, vaginal prog 200-mg daily 24 through 34 weeks)
  (RCT, n=458, CL 10-20 mm, vaginal prog 90-mg daily 20-24 through 37 weeks)
  (meta-analysis of 5 RCTs, n=775, CL <25 mm, vaginal prog 90-200 mg daily)
Kaplan-Meier Plot of the Probability of Continued Pregnancy without Delivery among Patients Receiving Vaginal Progesterone as Compared with Placebo.

Progesterone reduces the risk of spontaneous delivery before 34 weeks by 44.2% (hazard ratio for progesterone, 0.57; 95% CI, 0.35 to 0.92; $P=0.02$). $P=0.49$ for the test of the proportional-hazards assumption.

I didn’t believe it then, and I don’t believe it now …
Progesterone and PTB

- Environment of healthy skepticism and vigorous debate about progesterone
  - Not all studies show a benefit
    - Grobman W, for MFMU Network. SMFM 2012 (abstract)
  - Does not work in multiple pregnancy
FDA approval
February 3, 2011
Not all ‘progesterone’ is created equal

- **Synthetic progestins**
  - Medroxyprogesterone acetate (depo-provera)
  - Norethindrone acetate

- **Natural progesterone**
  - Progesterone powder, capsules, vaginal gel
  - Progesterone injection (oil)
  - 17α-hydroxyprogesterone caproate (17P)
What is 17P?

- Natural metabolite of progesterone with no androgenic activity
- Produced by placenta, corpus luteum
- Does cross placenta to small extent
- Previously marketed as …
  - Delalutin ®
  - Hylutin ®
  - Prodrox ®
  - Hydrogest ®
Safety of 17P

- No evidence for teratogenic effects of 17P in humans, including genital malformations

  Schardein JL. *Teratology* 1980; 22:251-70

  (11.5 year follow-up of 988 children exposed in utero to progesterone vs controls)

  (Meta-analysis of 186 articles)

Safety of other progestins

- Progestin supplementation from 4-14 weeks of gestation in IVF patients is associated with an increased risk of hypospadias in a male offspring (OR, 3.7; 95% CI, 2.3-6.0)

Silver IR. Adv Exp Med Biol 2004; 545:45-72
Briggs MH. Int J Fertil 1982; 27:70-2
Is it time to recommend progesterone supplement?

ACOG believes that “… further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as … short cervical length, or positive test for fetal fibronectin”

“Unresolved questions remain …”

ACOG Committee Opinion No. 291, November 2003
ACOG Committee Opinion No. 419, October 2008
Questions

- Why does progesterone supplementation prevent only 1/3 of recurrent PTB?
- Which subgroups of women benefit (prior sPTB, short cervix, pPROM, twins)?
- Can progesterone help not only for prevention, but also for treatment?
- In women in whom it does work, how does it work at a molecular level?
Women with cerclage?

- 17P after placement of a cerclage has not been proven to be useful
  
  A secondary analysis of a single RCT (n=300) evaluating cerclage vs no cerclage for prior sPTB + cervical shortening (<25 mm) found a non-significant trend towards lower rate of PTB at 28 and 32 weeks in women on combined therapy (cerclage + 17P)

Women with PTL?

- No studies have given progesterone in the setting of acute preterm labor
- The use of progesterone in women who remain undelivered after an episode of acute preterm labor may be beneficial

(n=60; 17P 341 mg twice weekly vs observation; decreased PTB [OR 0.15; 0.04-0.58])

(n=70; prog 400 mg PV daily vs observation; prolonged latency but no decrease PTB)
Twins and short cervix?

- Recent meta-analysis of 5 RCTs including 775 twin pregnancies with CL <2.5 cm treated with / without vaginal progesterone (90-200 mg) showed ...
  - a non-significant reduction in PTB <33 weeks (30.4% vs 44.8%; RR 0.70, 95% CI 0.34-1.44)
  - but a significant reduction in composite neonatal morbidity and mortality (23.9% vs 39.7%; RR 0.52, 95% CI 0.29-0.93)

Biologic plausibility?

- Progesterone supplementation does not significantly alter circulating steroid levels
  
  

- Basal levels of progesterone in the maternal circulation far exceed that of Kd of the hPR
**Myometrium and cervix**
- Differentially regulate PR isoforms (Mesiano et al. JCEM 2002; Oh et al. AJOG 2005)
- Affect PR co-regulators / histone acetylation (Condon et al. PNAS 2003)
- Modulate miRNA-200 family and targets, ZEB1 / ZEB2 (Renthal et al. PNAS 2010)
- Interfere non-genomically with OT binding (Grazzini et al. Nature 1998)

**Placenta**

**Amniotic fluid**
- Upregulates an endogenous inhibitor of PLA₂ (Norwitz et al. AJOG 2000)

**Fetal membranes**
- Inhibits apoptosis (Luo et al. Reprod Sci 2010; Wang et al. SMFM 2011)
Conclusions

- PTB remains a major cause of perinatal morbidity and mortality
- Preventative strategies to date have been largely unsuccessful
- A number of primary preventative strategies appear promising, especially progesterone supplementation
Conclusions (cont)

- Progesterone is **not** a panacea for PTB
- Progesterone supplementation prevents PTB in some high-risk women
- If we can determine which women benefit and how it works, *then* we may be able to develop novel agents to address this problem across a wide spectrum of parturients
Preterm births, 1990-2010

% of births

Preterm birth <37 weeks’ gestation

CDC / National Center for Health Statistics, 2012