

Progesterone for the prevention of preterm birth in women with a short cervix

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Evidence for progesterone as a modulator of labor

- In vivo:
 - An increase in plasma estrogen and a decrease in plasma progesterone precedes the onset of labor in many mammalian species

Implications for preterm labor: May be related to a pathologically early progesterone withdrawal



Hypothesis: Exogenous progesterone will offset withdrawal and preterm delivery

Johnson et al

- RCT: 43 women with history of 2 SAB, 2 PTB < 36 weeks, or one of each
- 17-P 250mg IM weekly vs. placebo
- No uniform GA for starting therapy
- Included patients with cerclage

	17-P	Placebo	OR (95% CI)
EGA*	38.6 ± 1.4	35.3 ± 6.2	-----
PTB	11%	48%	0.14 (0.03-0.72)

*P = 0.03

Johnson et al, N Engl J Med 1975

Hauth et al

- RCT: 168 women on active military duty
- 17-P 1000 mg IM weekly vs. placebo
- Initiation of treatment 16-20 weeks

BW < 2500g:
17-P: 7.5%
Placebo: 9.0%
OR 0.81 (0.24 – 2.73)

Hauth et al. Am J Obstet Gynecol 1983

Issue with biologic plausibility

- There is no evidence of a fall in maternal plasma progesterone levels or P/E ratios before the onset of human labor, either term or preterm

The progesterone paradox

- Progesterone is still involved in labor and preterm labor, even though no differences in serum levels
 - “Functional” progesterone withdrawal
 - Paracrine-type function
 - Changes in the mediators of progesterone’s “message”

Progesterone: Anti-inflammatory mechanisms

- Progesterone withdrawal associated with inflammation-mediated preterm birth
 - LPS given to mice resulted in decreased progesterone levels followed by PTD (Fidel et al, 1998)
 - LPS-initiated fall in progesterone followed by increase in myometrial PGE2, which is implicated in PTD in mice (Zeng et al, 2002)

da Fonseca et al

- RCT: 142 women at “high risk” for preterm delivery (at least one previous PTD, prophylactic cerclage or uterine malformation).
- 100mg progesterone vaginal suppository daily vs. placebo
- Initiation of treatment at 24 weeks

Preterm delivery:
Progesterone: 13.8%
Placebo: 28.5%
OR 0.40 (0.17 – 0.94)

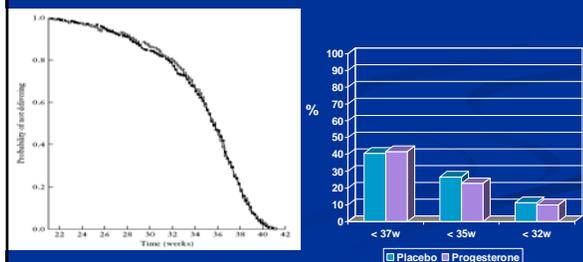
de Fonseca et al, Am J Obstet Gynecol 2003

da Fonseca et al

- **Study Issues**
 - Inclusion of women with CI and uterine malformations
 - Did not report any outcome other than PTD

Vaginal progesterone and PTD

- O'Brien et al, Ultrasound Obstet Gynecol 2007
- 659 women with prior sPTB randomized



Meis et al

- RCT: 463 women with a history of a spontaneous PTD
- 17-P 250mg IM weekly vs. placebo
- Initiation of treatment 16-20 weeks

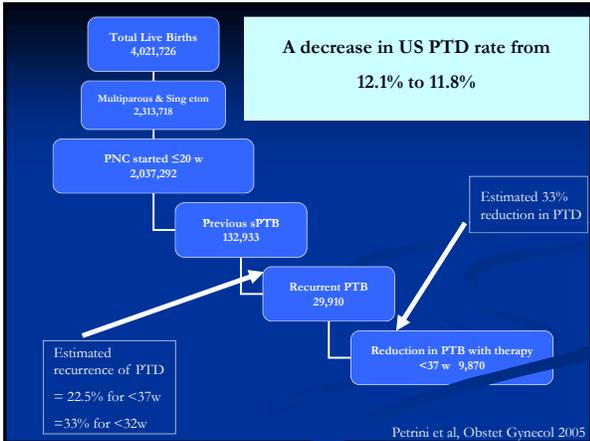
	17-P	Placebo	OR	NNT
PTB < 37 w	36%	55%	0.66 (0.54 – 0.81)	~6
PTB < 32 w	11%	20%	0.58 (0.37 – 0.91)	~12

Meis et al, NEJM 2003

Meis et al: Neonatal outcomes

	17-P	Placebo	OR
Necrotizing enterocolitis	0%	2.6%	P = 0.01
Any IVH	1.3%	5.2%	0.25 (0.08 – 0.82)
Supplemental O ₂	15%	24%	0.62 (0.41 – 0.92)
Retinopathy	1.6%	3.3%	0.50 (0.15 – 1.70)
BPD	1.3%	3.3%	0.40 (0.11 – 1.46)
Neonatal death	2.6%	5.9%	0.44 (0.17 – 1.13)

- ACOG Committee Opinion #291: Use of progesterone to prevent preterm birth
 - Recommended progesterone use for women with a prior spontaneous PTB



Can we extend the benefits of progesterone to other high-risk populations?

	EGA at study	Outcome	Discriminatory point	Overall PTD	Sensitivity	PPV
Jams et al N = 2915	24 weeks	< 35 weeks	25 mm (10 th %)	4.3%	37%	18%
Taipale et al N = 3694	18-22 weeks	< 37 weeks	29 mm (3 rd %)	2.4%	16%	13%
			31 mm (9 th %)		19%	5%
Hibbard et al N = 760	16-22 weeks	< 35 weeks	30 mm (10 th %)	6.7%	41%	27%
			< 37 weeks		11.2%	33%

Progesterone and short cervix

- Fonseca et al, NEJM 2007
 - RCT: 250 women with cervical length \leq 15mm
 - Progesterone 200 mg PV daily vs. placebo
 - Initiation of treatment at 24 weeks

	Progesterone	Placebo	OR (95%CI)
PTD < 34 weeks	21%	36%	0.56 (0.36 0.86)
Composite morbidity	8%	14%	0.59 (0.26 1.25)

Progesterone and short cervix: Fonseca et al

- Issues:
 - Very heterogeneous study group
 - Includes women with prior PTD, multiple gestations
 - Very short cervix (1.7% of the population, less in lower risk women)
 - Use of vaginal progesterone

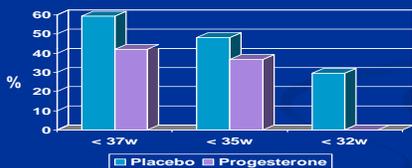
Accompanying editorial: Not yet indicated to use progesterone for women with a short cervix

Progesterone and short cervix

- DeFranco et al, Ultrasound Obstet Gynecol 2007
 - ~~Planned randomized trial of women with short cervix ≤ 25 mm and no history of PTB (no parallel with O'Brien trial of 2007)~~
 - ~~0 patients~~
 - Secondary analysis that included women with short cervix and prior preterm delivery
 - 25 mm did not provide enough patients for analysis
 - Explored other definitions of short cervix
 - Initially defined as that in the lowest quartile (32 mm)
 - Survival curves no different based on study medication (P = 0.34)
 - Assessed cutoffs of 30 and 28 mm as well
 - No significant difference in survival curves at either of these cutoffs
 - Further evaluated dichotomous outcomes at 28 mm

Progesterone and short cervix

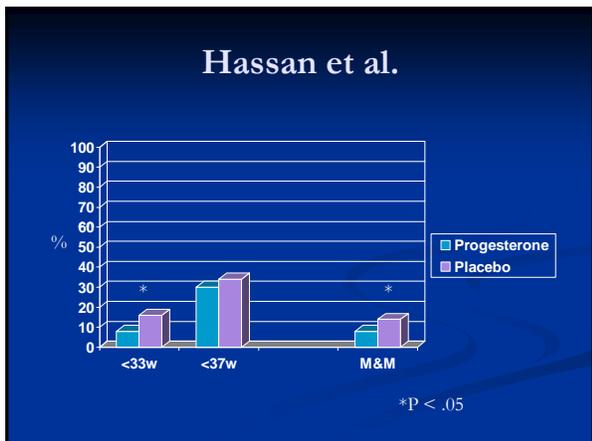
- 46 women with ≤ 28 mm cervical length
 - 19 progesterone
 - 27 placebo



"...these conclusions must be considered tentative...(and) hypothesis generating... (and)... further investigation is necessary. Specifically randomized clinical trials designed to test the effect of progesterone in women with short cervix..."

Progesterone and a short cervix: Hassan et al, 2011

- 19 to 23 6/67 weeks
- Singleton
- Cervix 10-20 mm
- Nullips and multips (with prior term and preterm birth)
- Outcome: PTB < 33 weeks
- N = 465



- ### Hassan et al.
- 60 women were enrolled in violation of protocol
 - 55 of these were with respect to EGA at enrollment
 - Significantly more women who were enrolled early randomized to placebo
 - Significantly more women who were enrolled late randomized to progesterone

- ### What are we left with?
- Good evidence that progesterone reduces frequency of recurrent preterm birth
 - Several properly powered + 17OHP trials
 - Brazilian vaginal progesterone trial + / US based vaginal progesterone trial
 - Progesterone for this indication will make little dent in the burden of preterm birth

What are we left with?

- A short cervix is associated with preterm birth
- Definition of short varies with gestational age
- Two studies of vaginal progesterone for reduction of PTB in women with a short cervix
 - Anyone with cervix < 15 mm (1%)
 - Singletons with cervix 10-20 mm (2%)
 - Issues with protocol violations
 - Ideal formulation, cervical length, GA at initiation, and certainty of benefit remain uncertain
