Prenatal Progesterone for Preventing Preterm Birth
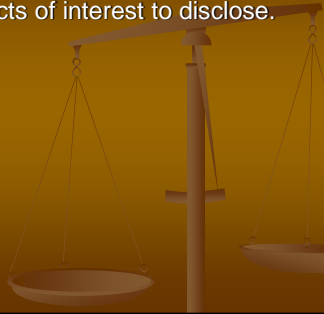
This activity is jointly-provided by SynAptiv and the Colorado Hospital Association

Safe Deliveries Project Partnership

- Colorado Hospital Association
- Anthem Blue Cross and Blue Shield Foundation
- March of Dimes Colorado/Wyoming Chapter
- Colorado Perinatal Care Quality Collaborative

Thomas J. Garite, M.D.

- I have no conflicts of interest to disclose.

Impact of Prematurity

- 300,000 premature births/year
- Accounts for 60-70% of perinatal mortality
- Accounts for about 2/3 of cerebral palsy
- Accounts for 50% of total $$ spent on all of obstetric and newborn care in the U.S.
- Probably now most common reason for antepartum hospitalization
- No impact since records have been kept, rate is actually rising in the past 5-10 years
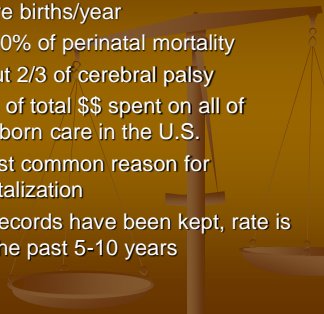
What does not work to prevent prematurity in at risk patients

Singletons
- Bed rest
- Prophylactic tocolytics
- Home uterine activity monitoring
- Baby ASA
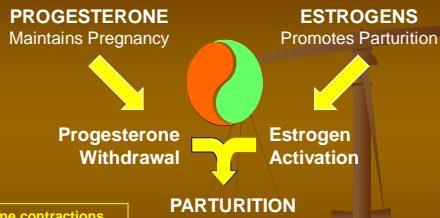- Antibiotics
- Risk Scoring and intensive antenatal surveillance

Twins
- Bed rest
- Cervical cerclage (routine)
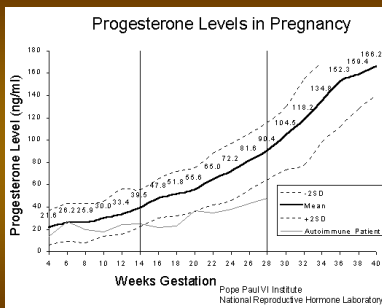- Multifetal reduction
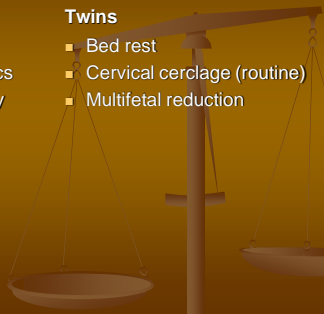
Progesterone as an option for the prevention of prematurity

Endocrine Control of *Parturition*

PROGESTERONE
Maintains Pregnancy

ESTROGENS
Promotes Parturition

Progesterone Withdrawal

Estrogen Activation

PARTURITION

- Uterine contractions
- Cervical ripening
- Rupture of membranes

Progesterone Levels in Pregnancy

Progesterone Level (ng/ml)

Weeks Gestation

Pope Paul VI Institute
National Reproductive Hormone Laboratory

-2SD
Mean
+2SD
Autoimmune Patient

3

Progesterone

- Critical in the activation of Estrogen to continue the cascade leading to labor is the reduction in the inhibitory effects of progesterone
- Unlike estrogen, the only apparent reason for the massive production of progesterone by the placenta is to inhibit the rapidly expanding uterus from going into labor prematurely
- Removal of progesterone in animals leads to the onset of labor

Physiologic Effects of Progesterone which allows labor inhibition

- Inhibits oxytocin activation of myometrium
- Directly inhibits prostaglandin production
- Decreases myometrial excitation
- Inhibition of gap junction formation

Prevention of Miscarriage with Progestins Meta-Analysis
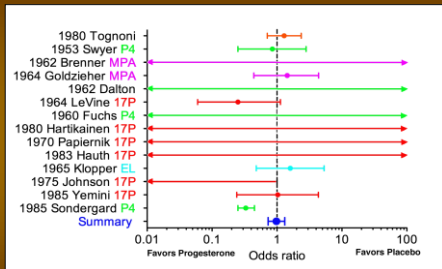
14 Trials, total N = 1400
MPA = medroxyprogesterone acetate, EL = Enol Luteovis
Tognoni used 17P+allyloestrenol

Plotted from Data in:
Goldstein et al., Br J Obstet Gynecol 96:265-74, 1989

Prevention of Preterm Birth with 17Pc, Meta-Analysis

	Year	Risk Factor	17Pc Dose	Frequency	Rx Start	Rx Stop
Johnson	1975	2 or more PTBs and/or SABs	250 mg	Weekly	At booking	37w
Papiernik	1970	High PTB risk score	250 mg	Q 3 days	28-32w	8 doses
Hartikaini n	1980	Twins	250 mg	Weekly	28-33w	37w
Yemini	1985	2 or more PTBs and/or SABs	250 mg	Weekly	At booking	37w
Levine	1964	3 or more SABs	500 mg	Weekly	< 16w	36w

Keirse, Br J Obstet Gynecol 97:149-54, 1990

Prevention of Preterm Birth with 17Pc, Meta-Analysis
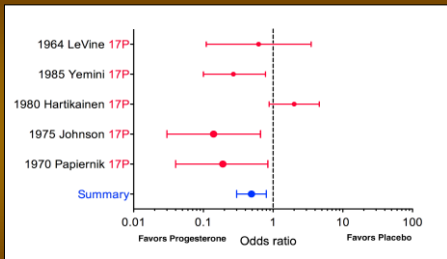
5 studies, Total N = 338
Summary OR = 0.49 (CI 0.3 to 0.8)

Keirse, Br J Obstet Gynecol 97:149-54, 1990

The NEW ENGLAND JOURNAL of MEDICINE
June 24, 2003

- **Prevention of Recurrent Preterm Delivery by alpha 17 hydroxy Progesterone Caproate**

Paul J. Meis, Mark Klebanoff, Elizabeth Thom, Mitchell Dombrowski, Baha Sabai, Atef Moawad, Catherine Spong, John Hauth, Menachem Miodovnik, Michael Warner, Kenneth Leveno, Steve Caritis, Jay Iams, Ronald Wapner, Deborah Conway, Mary J. O'Sullivan, Marshall Carpenter, Brian Mercer, Susan Ramin, John Thorp, Alan Peaceman for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

Multicenter RCT of Progesterone

- All patients with h/o previous preterm delivery due to PTL or PPROM
- Randomized between 15 and 20 3/7 weeks
- Singletons only
- Given trial placebo injection
- Started on weekly IM 17alpha OH Progesterone Caproate or placebo (2:1 randomization) until 36 weeks.

Multi-center RCT of Progesterone

- **Randomized 463 women (310 Prog., 153 Plac.)**
- **Preterm Delivery:**
  - **36% Progesterone**
  - **55% Placebo (P < 0.001)**
- **Delivery before 35 weeks**
  - **21% Progesterone**
  - **31% Placebo (P= 0.02)**
- **Delivery before 32 weeks**
  - **11% Progesterone**
  - **20% Placebo (P= 0.02)**
- **Borderline statistically significant reduction in neonatal death, ventilatory support, IVH, any O2 requirement**
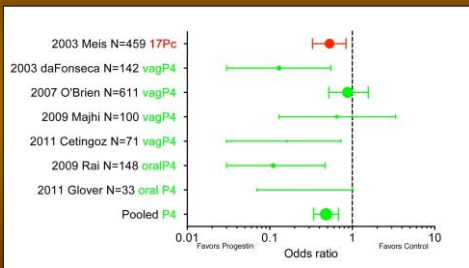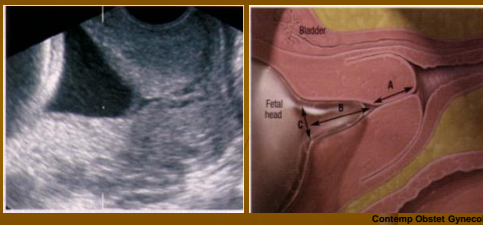
Fonseca et al: Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind trial:
Am J Obstet Gynecol 2003;18:

- Randomized patients with previous spont. preterm delivery, cerclage, uterine anomaly
- 100 mg progesterone suppositories or placebo every night from 24 to 34 weeks
- 142 patients randomize (70 Prog vs. 72 Plac.)

Fonseca et al: 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 trial:
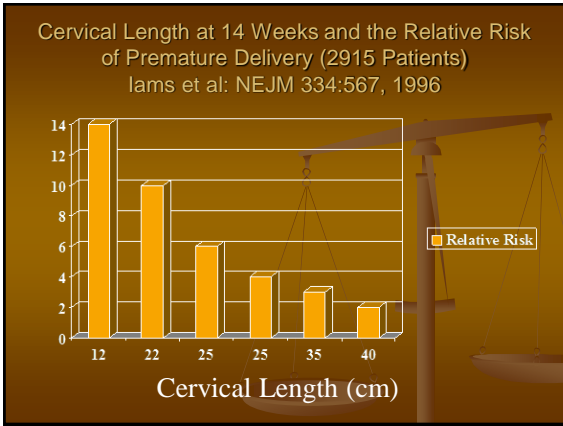Am J Obstet Gynecol 2003;18:

- **Results**
  - **Preterm Delivery**
    - **Progesterone 14%**
    - **Placebo 29% (p= 0.03)**
  - **Delivery < 34 weeks**
    - **Progesterone 3%**
    - **Placebo 19% (p= 0.002)**
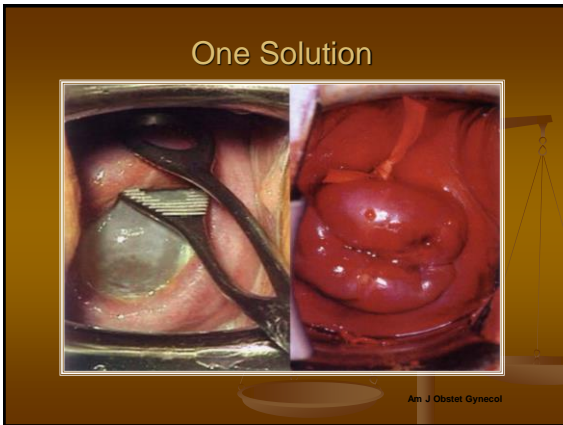 - **Admitted for Preterm Labor**
    - **Progesterone 19%**
    - **Placebo 31%**

Progestins for History of PTB
Recent Trials, PTB < 32 or <34 weeks

2003 Meis N=459 17Pc
2003 daFonseca N=142 vagP4
2007 O'Brien N=611 vagP4
2009 Majhi N=100 vagP4
2011 Cetingoz N=71 vagP4
2009 Rai N=148 oralP4
2011 Glover N=33 oral P4
Pooled P4

Odds ratio
Favors Progestin   Favors Control

Short Cervix – What to Do?

Bladder
Fetal head
Contemp Obstet Gynecol

Cervical Length at 14 Weeks and the Relative Risk of Premature Delivery (2915 Patients)
Iams et al: NEJM 334:567, 1996

Cervical Length (cm)

One Solution

Am J Obstet Gynecol

Cerclage for Short Cervix
Meta-analysis of 4 Randomized Trials

	Total N	PTB < 35w Cerclage	PTB <35w No Cerclage	RR
Singleton, Short Cvx, No Other Risk Factor	235	26%	33%	0.76
Singleton, Short Cvx, Prior PTB	208	23%	39%	0.61*
Twins, Short Cvx	49	75%	36%	2.15*

* P < 0.05

Berghella et al, Obstet Gynecol 106:181-9, 2005

8

Effect of Vaginal Progesterone on Pregnancy Outcome in Singletons with an Ultrasonically Short Cervix (5 RCT's)
## An Individual Patient Meta-analysis

Romero et al: Am J Obstet Gynecol 2011:206(2) 124

Romero et al, AJOG 2012
Individual Patient Data Meta-analysis

- 5 trials, 775 women, 827 infants
- Vaginal progesterone treatment for TVU CL ≤ 25 mm (asymptomatic)
- 42% reduction in PTB < 33 weeks
- 43% reduction in composite neonatal morbidity and mortality
- 25% significant reduction in NICU admissions
- No significant differences between treatment and placebo groups in rates of adverse maternal events or congenital anomalies
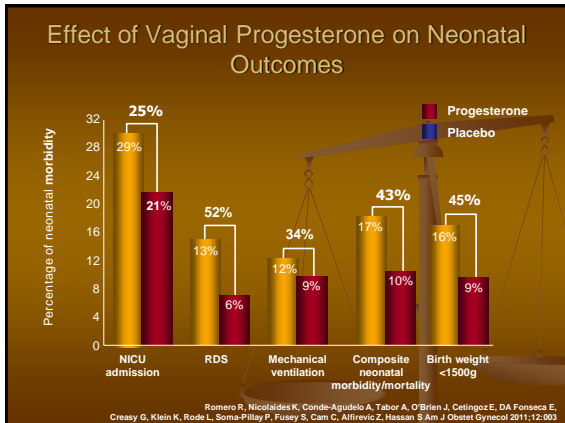
Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. , Am J Obstet Gynecol 2012;206:124.e1-19.

Results: Romero et al
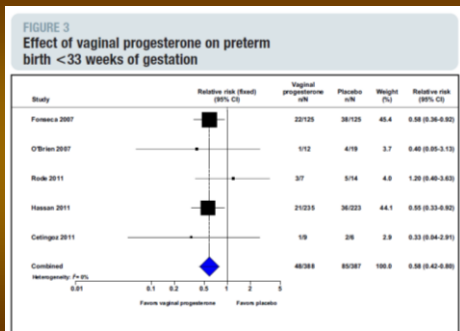
Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the mid trimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. , Am J Obstet Gynecol 2012;206:124.e1-

Primary Outcome

42% reduction in the rate of preterm birth <33 weeks

Effect of Vaginal Progesterone on Neonatal Outcomes

Legend: Progesterone, Placebo

Percentage of neonatal morbidity

- NICU admission: **25%** (29%, 21%)
- RDS: **52%** (13%, 6%)
- Mechanical ventilation: **34%** (12%, 9%)
- Composite neonatal morbidity/mortality: **43%** (17%, 10%)
- Birth weight <1500g: **45%** (16%, 9%)

Need to Treat for Benefit

- Vaginal progesterone for short cervix
  - Treat 11 patients to prevent 1 PTB < 33 weeks
  - Treat 14 patients to prevent 1 case of RDS
- Magnesium sulfate for pre-eclampsia
  - Treat 100 patients to prevent 1 case of eclampsia
- Antenatal corticosteroids during preterm labor
  - Treat 13 patients to prevent 1 case of RDS

The Effect of Vaginal Progesterone on the Primary Outcome According to whether Patients had a Previous Preterm Birth

	Preterm birth before 33 weeks gestation		
	n	RR (95% CI)	Interaction p value
Obstetric history			0.68
With no previous preterm birth	606	0.61 (0.42-0.89)	
With ≥1 previous preterm birth	169	0.54 (0.30-0.98)	

Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien J, Cetingoz E, DA Fonseca E, Creasy G, Klein K, Rode L, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan S Am J Obstet Gynecol 2011;12:003

The Effect of Vaginal Progesterone on Composite Neonatal Morbidity/Mortality According to Whether Mothers had a Previous Preterm Birth

	Composite neonatal morbidity/mortality		
	n	RR (95% CI)	Interaction p value
Obstetric history			0.40
With no previous preterm birth	658	0.62 (0.43-0.91)	
With ≥1 previous preterm birth	169	0.41 (0.17-0.96)	

Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien J, Cetingoz E, DA Fonseca E, Creasy G, Klein K, Rode L, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan S Am J Obstet Gynecol 2011;12:003

Does the effect of vaginal progesterone vary as a function of cervical length?

	<10mm	10-20mm	21-25mm
PTB	0.83(0.49–1.41)	0.52(0.35–0.76)	0.50(0.10–2.41)
Comp NN Morb	0.62(0.28–1.38)	0.54(0.35–0.84)	0.89(0.33–2.36)

Romero R Hassan S

Slide 1

Does the response to vaginal progesterone vary according to the dose used in the different trials?

Romero R Hassan S

Slide 2

	Composite neonatal morbidity/mortality		
	n	RR (95% CI)	Interaction p value
Daily dose of vaginal progesterone			0.92
90-100 mg	511	0.58 (0.35-0.95)	
200 mg	316	0.56 (0.34-0.94)	

Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien J, Cetingoz E, DA Fonseca E, Creasy G, Klein K, Rode L, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan S Am J Obstet Gynecol 2011;12:003

Slide 3

Romero et al IPD Meta-analysis Progesterone for Women with Short Cervix

- Reduction in rates of spontaneous premature delivery at all gestational ages from < 28 to < 37 weeks.
- Impact greatest in preventing PTD at the very earliest gestational ages
- Impact in women with Cervical lengths < 10-25 mm, but only in subgroups 10-20mm
- Reduction seen in women with and without a history of previous preterm delivery
- No significant reduction in twins (underpowered/positive trend

Vaginal Progesterone – The OPPTIMUM Study
Norman et al: Lancet on line Feb 23, 2016

- Multicenter RCT in UK of patients with either a short cervix (<25mm) or a previous PTB
- Randomized 1228 women daily 200mg vaginal P vs. placebo
- Outcome
  - Delivery < 34 weeks:
    - P 16.0% Placebo 18.1% (0.64-1.17)
  - Outcomes
    - NN Morbidity or Death: P 6.6%, Placebo 10.2% (0.38-1.03)
    - NN Death: P 0.01%, Placebo 1.0% (.06-.49)
    - Mod. to Severe Neurologic Impairment: P 12%, Placebo 9% (0.98-2.15)

Universal Cervical Length Screening? Cost-Benefit Analysis

Assumptions (based on Fonseca data)
  Singleton
  Prior PTB cases (7.3%) would get 17Pc if no TVCL
  One TVCL screen during anatomy scan, cost $52
  TVCL < 15 mm in 1.2% of population
  Vaginal P4 will reduce PTB<34 weeks from 30% - 18%

Results (per 100,000 women screened)
  $125 Million saved
  200 quality-adjusted life-years gained
  141 cases of serious neonatal morbidity prevented
  Universal screening better than screening targeted at women with prior PTB

Cahill et al, AJOG 202:548.e1-8, 2010

Universal Cervical Length Screening? Cost-Benefit Analysis

Assumptions (based on Fonseca data)
  Singleton
  No prior PTB
  Single TVCL screen at 18-24 weeks, cost $187
  TVCL < 15 mm in 1.7% of population
  Vaginal P4 will reduce PTB<34 weeks from 32% to 17%

Results (per 100,000 women screened)
  $12.1 Million saved
  434 quality-adjusted life-years gained
  22 neonatal deaths or neuro deficit prevented
  Robust across wide range of costs & assumptions

Werner et al., Ultrasound Ob Gyn 2011

13

Transabdominal Ultrasound

- Designed to image the baby
- Routine fetal anatomy scan at 18-22 weeks
  - Protocol includes looking at the cervix
  - Full bladder often elongates and distorts cervix
- Per ACOG/SMFM
  - Not reliable nor reproducible as a screening method
  - Not sufficient evidence to suggest benefit of TAU screening for progesterone or other intervention

---

Friedman et al: Can transabdominal ultrasound be used as a screening test for short cervical length? AJOG 2013 208 (3):190
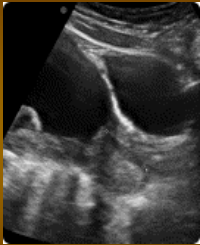
- Screened 1217 Patients at 16-24 weeks with both TA and TV US
- 76 had a TV CL <= 25 mm
- To have a 96% confidence of identifying these 76 women they needed to have a TA CL of <= 36 mm
- 6.2% could not be screened due to technical difficulty
- 54% (657/1217) had a TA CL <36 mm
- **So with screening with TA US you will still need to do TV on 60% of women to identify almost all women who will have a TV CL of <25mm**

Transvaginal Ultrasound

- Designed to image the reproductive organs
  - Identify anomalies
  - Diagnose complications (e.g., cervical shortening, funneling, amniotic sludge or debris)
- Used in clinical trials of vaginal progesterone
- Per ACOG/SMFM
  - Diagnostic exam for intervention
  - Proper technique, quality control, monitoring essential
  - Certification recommended
- Perinatal Quality Foundation
  - 3 lectures
  - Exam
  - Image review
  - CME credit

CIeaR
Cervical Length Education and Review
https://clear.perinatalquality.org/

The Arabin Pessary for the Prevention of PTB with a Short Cervix
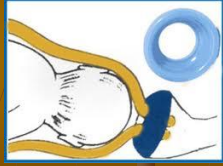
Two Large RCT's of Pessary for a Short Cervix

- PECEP Study (Goya et al:Lancet 2012;379, 1800-06.
  - 385 women with CL < 25mm
  - Delivery < 34 weeks (primary outcome)
    - 6% pessary, 27% control (RR 0.24, 0.13-0.43)
  - Delivery < 28 weeks
    - 2% pessary, 8% control (RR 0.24, 0.09-0.73)
- Hui (Am J Perinat 2013 Apr;30(4):283-8
  - 108 women with CL <25
  - Delivery < 34 weeks
    - 9% pessary, 6% control

RCT of Pessary in Twins
Liem et al: Lancet, 2013 382:1341

- RCT of all women with multiple pregnancy
- 40 Hospitals in the Netherlands
- 403 pessary, 410 control
- No overall difference in preterm birth or composite overall outcome
- In women with cervical length < 25th %
  - Composite nn morbidity - 12% pessary, 29% control(RR 0.42, (0.19-0.91)
  - PTD < 32 weeks – 12% pessary, 28% control (RR 0.43, 0.21-0.89

Recent RCT of Pessary in Twins
Nicolaides et al: AJOG 2016

- Randomized unselected twins to pessary at 20-24 weeks vs. routine care
  - N = 1180 (590 in each group)
- No differences in outcome
  - Delivery < 34 weeks – 13.6% vs. 12.9%
  - Adverse NN outcome – 10.0% vs. 9.2%
- Subanalysis of 214 women with a short cervix <25mm showed not benefit either

Bioteque Cup Pessary

Available in the U.S., Bioteque, Inc. San Jose, CA
FDA approved for use in pregnancy

Society Guidelines:
Progesterone to Prevent Preterm Birth

SMFM   ACOG   ACNM

Recommendations for Routine Cervical Length Screening

- SMFM
  - The issue of universal TVU CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners
- ACOG
  - Although this document does not mandate universal cervical length screening in women without a prior preterm birth, this screening strategy may be considered. Practitioners who decide to implement universal cervical length screening should follow one of the protocols for transvaginal measurement of cervical length from the clinical trials on this subject
- ACNM
  - Application of evidence based strategies to effectively screen women at potential risk for preterm birth should be accessible and available to every woman including strategies to assess cervical length in order to implement timely prevention strategies

SMFM Recommendations

- In women with singletons, no prior ptb, <24 weeks with cervical length < 20 mm, vaginal progesterone 90 or 200 mg is associated with a reduction in PTB and PN morbidity and mortality and can be offered in these cases
- The issue of routine screening of all pregnant women is a subject of debate but such a screening strategy can be viewed as reasonable…..
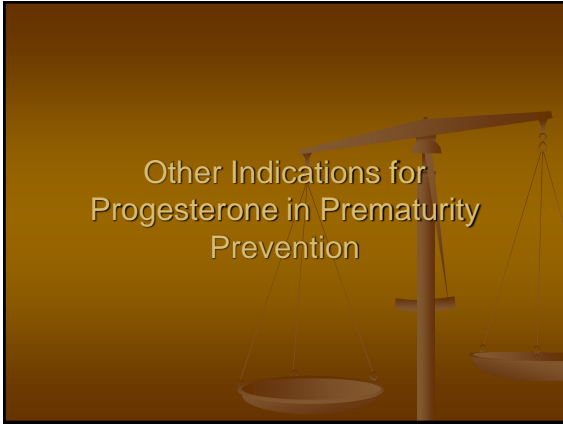
SMFM Recommendations (cont.)

- In singleton pregnancies with a prior (spontaneous) PTB prior to 37 weeks, 17 OH Prog caproate 250 mg IM q week starting at 16-20 weeks until 36 weeks is recommended
- In these women with a prior PTB and whom the cervix shortens to < 25 mm, cervical cerclage may (also) be offered.
- Progesterone has NOT been associated with a reduction in PTB in patients with multiple pregnancy, preterm labor or PPROM
- Transabdominal screening for cervical length is not recommended.

FIGURE
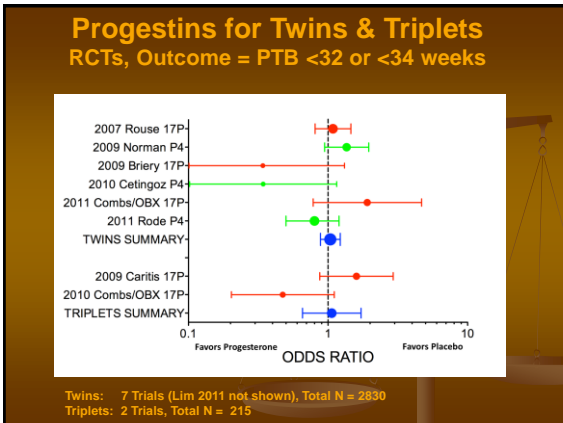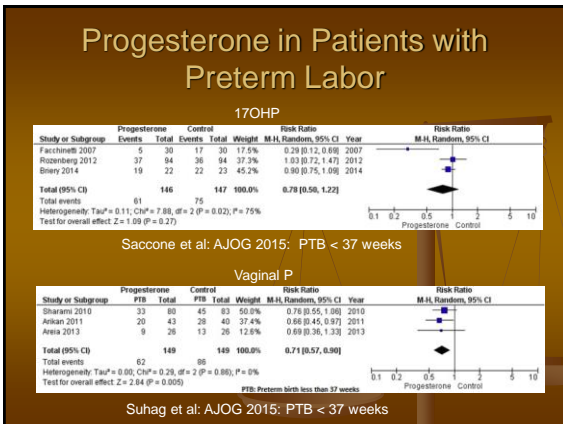Algorithm for use of progestogens in prevention of PTB in clinical care
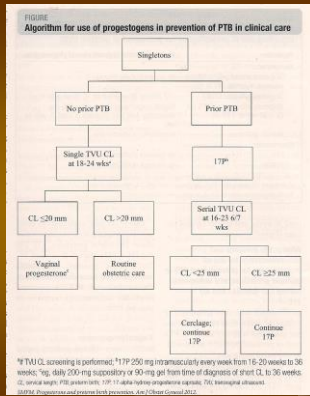
What are the concerns with routine endovaginal ultrasound screening?

- Lack of training and consistency in doing transvaginal US for cervical length
- "Indication Creep"
- What to do with 20-25 mm
- Lack of availability in some areas
- Applies to only about 2% of women
- Many ultrasounds for those needed to treat

Other Indications for Progesterone in Prematurity Prevention

Progestins for Twins & Triplets
RCTs, Outcome = PTB <32 or <34 weeks

Twins: 7 Trials (Lim 2011 not shown), Total N = 2830
Triplets: 2 Trials, Total N = 215

Progesterone in Patients with Preterm Labor

Saccone et al: AJOG 2015: PTB < 37 weeks

Suhag et al: AJOG 2015: PTB < 37 weeks
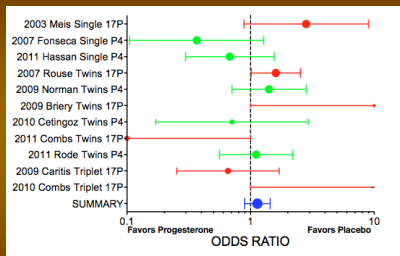
Progesterone for PPROM
RCT of patient with PPROM
23 – 31 weeks
17OHP Weekly vs. Placebo
Combs, Garite et al: AJOG2015

Safety Issues

www.vanityfair.com
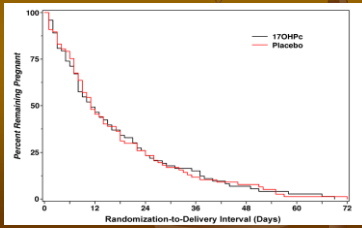
Perinatal Losses with Progestins
(Miscarriages < 20 weeks, stillbirths, neonatal deaths)

11 placebo-controlled trials, Total N = 6166 offspring.
3.5% Losses with Progestin
3.1% Losses with Placebo

NO EVIDENCE OF TERATOGENICITY

Followup, Mean Age 48 months
From Meis 2003 Trial, history of prior PTB

Scores below Cut-off on Ages & Stages Questionnairre	17Pc (n=193)	Placebo (n=82)	P
Communication	11%	11%	NS
Gross motor	3%	4%	NS
Fine motor	21%	18%	NS
Problem-solving	10%	11%	NS
Diagnoses from Health Prof'l			
Motor skills problem	1%	1%	NS
Developmental delay	7%	8%	NS
Attention or learning problem	8%	10%	NS

Northen et al, Obstet Gynecol 110:865-72, 2007

Long Term Follow up of Babies from Progesterone Trials

- Rode et al n(2011): US Ob Gyn: N = 433. Mean ASQ scores at 6 months and 18 months were not significantly different between the two groups (215 for infants in the progesterone group and 218 for infants in the placebo group at 6 months (P = 0.45) and 193 and 194, respectively, at 18 months (P = 0.89)).
- McNamara et al (2015): N=759 There was no evidence of difference between the progesterone and placebo groups in global health status assessed using the Health Utilities Index
- O'Brien et al (2011): N=229-445. Developmental f/u and morbid condition comparison at 6, 12 and 24 months, no difference
- Norman et al (2016): 869 no difference

| Cognitive Composite score at 2 years, mean (SD) | 97.7 (17.5)[b] n=439 | 97.3 (17.9)[c] n=430 | 0.48 (-2.77, 1.81) | 0.680, p$_{adj}$=0.680 |

Progesterone Costs

- Makena (17OHP)
  - Retail $680/dose, copay about $70
  - Compounded – generally not available due to FDA bulletin
- Vaginal Progesterone
  - Crinone gel – about $15/day
  - Prometrium – about$1/day
  - Compounded Progesterone – cheap if available

Summary

- Progesterone lowers the rate of premature delivery and avoids many associated morbidities in:
  - Patients with a history of a prior PTB
  - Patients with a short cervix
  - In patients with a short cervix and a prior preterm birth both a cerclage and progesterone used together creates the optimum outcome
- Progesterone does not lower the rate of preterm birth in patients with multiple gestations
  - The jury is out on those with short Cervix
- Vaginal ultrasound for cervical length may become routine in all pregnant women
- Based on available data, progesterone is safe.