A Contemporary Approach to the Prevention of Preterm Birth

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Conflict of Interest

• I hold stock in and serve on the Scientific Advisory Board for Sera Prognostics
• I will not discuss the products sold by Sera Prognostics in this presentation
Case 1

• 39 year old G4 P 1021 at 12 weeks gestation presents for prenatal care
  – OB history:
    – 1) Term uncomplicated vaginal delivery
    – 2) First trimester SAB
    – 3) PPROM at 18 weeks gestation
      • induced secondary to concern for chorioamnionitis
      • Vaginal delivery after 4 hours of induction

• What is her risk for preterm birth?
• What if any interventions should she be offered?
Preterm Parturition

The new definition
Classic View

Uterine contractions + cervical change = Labor

New Thought

Cervical change

Uterine Contractions
Preterm Birth 101

If You Trained Before 2012, You Had To Take This Course
If You Trained After 2012, You Might Still Have Taken This Course

Where Were Your Teachers Standing When They Wrote The VERSUS Chapters?

• Preterm Labor
  VS.  Contractions ➔ Cervical Change ➔ PTB

• Preterm PROM
  VS.  Ruptured Membranes ➔ Labor ➔ PTB

• * Cervical Insufficiency *
  VS.  Cervix weak, dilates ➔ Baby falls out

• Abruption
  VS.  Bleeding ➔ Contractions ➔ Labor ➔ PTB
3 Steps of Parturition

- Cervical ripening
- Decidual-membrane activation
- Uterine contractions
  - Order of these steps can be determined by history
  - Symptoms of cervical ripening and Decidual/membrane activation include:
    - Pelvic pressure
    - Menstrual like cramping
    - Increased vaginal discharge
    - Advanced cervical dilation with minimal contractions
New View of PTB
Parturition Not Labor

• Not “Contractions lead to cervical change”
  – Uterine contractions are not the primary driver in most cases
• Cervical ripening and endometrial activation are first step of preterm parturition
• Progesterone slows these steps
  – Very preterm birth
  – Inflammation
• Cerclage may be beneficial in some cases
  – Short cervix < 24 weeks
  – Prevent membrane prolapse and bacterial invasion
• Parturition may begin prior to 20 weeks
  – Blurs the lines between miscarriage and PTB
  – Losses as early as 16 weeks gestation may be sPTB
New View of PTB

• Cervical ripening
  – Begins in early second trimester – as early as 16 weeks
  – Driven primarily by inflammation
  – Most common presentation

• Classic cervical insufficiency and classic spontaneous PTB overlap

• Spontaneous births at 16-20 weeks should probably be included with those between 20-36 weeks
Pregnancy outcome after second trimester loss

Who is at risk?

Identification of high risk patients is the first step in prevention.
Risk Factors for Preterm Birth

• The strongest risk factor for a PTB is a previous history of PTB
  – Risk is affected by number of previous PTBs and gestational age of previous deliveries
  – The most recent delivery is best predictor of the outcome of the current pregnancy
  – Even a previous PTB in a twin pregnancy is associated with an increased risk in the current pregnancy
    • 40% chance of PTB when the twin pregnancy delivered prior to 30 weeks gestation

Esplin et al. Obstet Gynecol 2008; 112 (3)
Facco et al. Am J Obstet Gynecol 2007; 197
Additional Risk Factors

- Major risk factors
  - Multiple Gestation
  - Short cervix
- Minor risk factors
  - Race – African American race
  - Previous cervical /Uterine surgery
    - Conization and LEEP
  - Short interpregnancy interval
  - Low prepregnancy BMI
  - History of multiple SAB
  - Smoking
  - Vaginal bleeding
Focus on women with a history of SPTB
Impact of Recurrent Preterm Birth

• 15% of all preterm births are recurrent preterm births
  – 75,000 of the 500,000 PTB in the US annually

• Interventions including progesterone reduce rate by up to 30%
  – Estimated that 10,000 PTB prevented annually*

• The only type of PTB that can be accurately predicted

The utility of an obstetric history

How to take one
Obstetric History

• Rule out cervical insufficiency
• Provide a personal estimate of risk
  – Number and severity of preterm births
  – Identify non-recurrent causes of preterm birth
  – Identify potential etiologies
• All preterm births are not created equal
  – Need to know clinical circumstances of previous delivery
Assessment of Risk

• Number and timing of preterm births
  – Use Utah chart
  – Consecutive PTB
• Evidence of inflammation in previous delivery
  – Modification
• Non-recurrent cause of preterm birth
• Family history of preterm delivery
  – Modification
• Presence of other risk factors
  – Hypertension
  – Drug use
  – Prior spontaneous abortions
  – Cervical surgery
Proportion of Preterm Births (<37 weeks) in a Woman's 1st, 2nd, and 3rd Birth Excluding Women with Any Indicated Preterm Inductions (n=17410)

First Birth

- **Term**
  - n=15947
  - 91.60%

- **Preterm**
  - n=1463
  - 8.40%

Second Birth

- **Term**
  - n=14908
  - 93.48%

- **Preterm**
  - n=1039
  - 6.52%

- **RR=1.00**

Third Birth

- **Term**
  - n=14039
  - 94.17%

- **Preterm**
  - n=869
  - 5.83%

- **Term**
  - n=762
  - 73.34%

- **Preterm**
  - n=277
  - 26.66%

- **RR=1.00**

- **RR=4.81 (4.1-5.2)**

- **Term**
  - n=762
  - 73.34%

- **Preterm**
  - n=277
  - 26.66%

- **RR=2.95 (2.4-3.2)**

- **Term**
  - n=895
  - 83.88%

- **Preterm**
  - n=172
  - 16.12%

- **RR=7.93 (7.0-9.0)**

- **Term**
  - n=213
  - 53.79%

- **Preterm**
  - n=183
  - 46.21%
Personal Risk

• 3 historical factors that affect risk
  – Race – African American race increases risk 1.5 – 2.0 fold
  – Number of previous preterm births
    • Each increases risk by 1.5 fold
  – Gestational age of the index preterm birth
Risk of recurrent preterm birth

Prior preterm delivery status by order and gestational age at delivery

Risk of recurrent preterm birth in 19,025 women with 2 prior preterm births according to the order and gestational age of the previous preterm births.
Personal Risk

• Provides motivation to the patient to be compliant
• Patient will take symptoms seriously
• Staff understand the importance of vigilant care
Case 1

• What is the risk of recurrent PTB?
  – 20-25%
Screening tests

Does anything really help?
Screening

• Infection/inflammation
  – Asymptomatic bacteruria
  – Bacterial vaginosis

• Cervical length
Asymptomatic Bacteruria

• Meta-Analysis of 14 randomized trials
• Antibiotic therapy associated with
  – Decreased continued ASB OR 0.07 (95%CI 0.05-0.1)
  – Decreased pyelonephritis OR 0.24 (95%CI 0.19-0.3)
  – Decreased PTB and LBW OR 0.6 (95% CI 0.4-0.8)

Smaill et al. Cochrane Database 2001
Bacterial Vaginosis Treatment

• Meta-analysis of high risk patients
  – History of previous preterm birth
• 2 trials of 114 women
  – PPROM OR 0.14 (95% CI 0.05-0.38)
  – LBW OR 0.31 (95% CI 0.13-0.35)
  – Recurrent PTB OR 0.83 (95% CI 0.59-1.17)

McDonald et al. Cochrane Database 2007
Cervical Length

• Cervical length decreases up to 6-8 weeks prior to delivery
  – Rate of change may be as important as absolute length

• Cervical remodeling is the most common first step in the parturition process

• Objective measure
  – Consider the rate of change as well

• Can direct interventions
Primary Risk Factors for SPTB

• History of SPTB
• Short Cervix

• What do we have to offer these women?
The role of progesterone

Which type and when
Prevention Strategies

• **Primary Prevention**
  – Provide prenatal care to general population to prevent disease

• **Secondary Prevention**
  – Provide care for high-risk patients who do not have symptoms of active disease

• **Tertiary Prevention**
  – Treatment of patients after the onset of symptoms
Progesterone
The new (old) option

• Why would this work?
  – Progesterone decreases the inflammatory response
  – Potent smooth muscle relaxant
    • Blocks the effect of prostaglandin-F2α and oxytocin
  – Some suggest there is a decrease in the progesterone to estrogen ratio at time of delivery
Actions of Progesterone on the Myometrium

- Decreases conduction of contractions
- Increases threshold for stimulation
- Decreases spontaneous activity
- Decreases number of oxytocin receptors
- Prevents formation of gap junctions
Confusion About Progesterone

- Does not work on all patients
  - Only prevents one third of recurrent SPTB
- Not all studies demonstrate benefit
- Indication creep – who is really a candidate
  - Twins
  - History of PPROM, Abruption, twin SPTB
- Multiple options for treatment
  - Vag P versus 17 OHCP
- Optimal timing for treatment
Progesterone
The new (old) option

• 5 Studies performed between 1964 and 1985
  – 3 positive effect
  – 2 negative effect
• Studies were limited by small numbers and contradictory findings
• Women were treated for different indications
• Different type, dosages and routes of administration of progesterone were used
Progesterone
The new (old) option

• Meta-analysis (1990) 7 randomized controlled trials (1964-1985)
  – Only 17 alpha Hydroxyprogesterone caproate (17 OHPC)
  – Women enrolled for either risk of recurrent SAB or previous PTB

Keirse MJ. BJOG 1990 Feb;97(2):149
Progesterone
The new (old) option

• Meta-analysis (1990) 7 randomized controlled trials (1964-1985)
  – Reduction in rates of preterm birth. Odds ratio was 0.50, 95% CI: 0.30-0.85
  – Reduction in rates of low birthweight, Odds ratio was 0.46, 95% CI: 0.27-0.80
  – No difference in neonatal morbidity and mortality

Keirse MJ. BJOG 1990 Feb;97(2):149
# Preventing PTB in Singleton Pregnancies

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Indication</th>
<th>Progesterone</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keirse</td>
<td>1990</td>
<td>Hx of SPTB</td>
<td>17 OHPC</td>
<td>Decreased by 40%</td>
</tr>
<tr>
<td>Meis</td>
<td>2003</td>
<td>Hx of SPTB</td>
<td>17 OHPC</td>
<td>Decreased by 35%</td>
</tr>
<tr>
<td>Fonseca</td>
<td>2003</td>
<td>Increased risk</td>
<td>Vag P</td>
<td>Decreased by 35%</td>
</tr>
<tr>
<td>Fonseca</td>
<td>2007</td>
<td>Short cervix &lt;15 mm</td>
<td>Vag P</td>
<td>Decreased by 45%</td>
</tr>
<tr>
<td>O’Brien</td>
<td>2007</td>
<td>Hx of SPTB</td>
<td>Vag P gel</td>
<td>No difference *</td>
</tr>
<tr>
<td>Hassan</td>
<td>2011</td>
<td>Short cervix 10-15 mm</td>
<td>Vag P gel</td>
<td>Decreased by 45%</td>
</tr>
<tr>
<td>Grobman</td>
<td>2012</td>
<td>Short Cervix &lt;30 mm</td>
<td>17 OHPC</td>
<td>No difference ^</td>
</tr>
</tbody>
</table>

* Only 4% had cervical length < 25 mm

^ Most had cervical length 20-30 mm
Progesterone Therapy

• Meta-analysis of randomized trials
  – 7 trials of 17OHP to prevent recurrent PTB
  – Use 17 OHP 250 mg im weekly beginning at 16-20 weeks
  – Risk for PTB < 37 wks - 1020 women enrolled
    • RR = 0.58, 95% CI = 0.48-0.70
  – Risk for infant with birth weight of < or =2.5 kg - 872 infants
    • RR = 0.62, 95% CI = 0.49-0.78
  – Risk of an infant diagnosed with intraventricular hemorrhage -458 infants
    • RR = 0.25, 95% CI = 0.08-0.82
Vaginal progesterone resulted in reduction of SPTB from 22% (placebo) to 12% (treated)
Cervical Length in Women Enrolled In Studies of Progestin Prophylaxis of Preterm Birth

Probability of PTB < 35 Weeks in Untreated Women

PROGESTERONE WORKS

Fonseca Vag P

Hassan Vag P

Grobman 17 P

O’Brien Vag P

PROGESTERONE DOESN’T WORK

Curve drawn after data from Iams et al NEJM 1996
Results of the Progesterone Studies Define Phenotypes of Preterm Birth

Short Cx Spont PTBs Are *Progesterone*-Sensitive

Long Cervix Spontaneous PTB’s Are Not P Sensitive

Fonseca, Hassan (& Meis)

%’s are BPG’s
~ 30% of SPTB are preceded by Short Cervix

Take a History!

Indicated
Multifetal
Spont Not Short Cx
Spont Short Cx
17 OHPC versus Natural Progesterone

- In Human and Animal tissues
  - Cervix or decidua are likely targets
    - Vaginal administration - increased progesterone within gestational tissues
  - Natural progesterone stimulates gene expression within the reproductive tissues
    - Increased defensin-1 in cervix
    - Reduced macrophage population in decidua
    - Reduced MMP 9 + cells
  - 17 OHPC has significantly less direct effect
    - Has only 25-30% of binding affinity for progesterone A and B receptor compared to natural progesterone
    - Competes with progesterone for Cytochrome P450 3A4 enzyme – indirectly increases natural progesterone
Progesterone Therapy

• SPTB and serum 17 OHPC levels
• 315 women with history of SPTB on weekly 17 OHPC – 250 mg weekly
  – blood sample at 25-28 weeks
  – Plasma 17 OHPC concentrations ranged from 3.7-56 ng/ml
  – Women with plasma levels in lowest quartile had higher rate of SPTB and early GA at delivery
  – Lowest PTB rates occurred when plasma levels were > 6.4 ng/ml

Vag P vs. 17 OHPC

• Prospective randomized trial for women with history of SPTB
  – 90 mg vaginal progesterone gel daily (n=253)
  – 250 mg 17 OHPC weekly (n=249)
  – Started at 14-18 weeks

• Inclusion
  – Singleton between 14 and 18 weeks gestation
  – History of previous SPTB
    • Included women who had cerclage in previous pregnancy
Vag P vs. 17 OHPC

- Primary outcome GA at < 34 weeks gestation
  - Vag P 42/253 (16%)
  - 17 OHPC 64/249 (25.7%)
  - P = 0.02
  - OR 0.58 (95%CI 0.37-0.89)
17 OHPC versus Vaginal Progesterone

• Both work on women with a history of SPTB at risk for short cervix
• Data suggests that natural progesterone has a larger direct effect on gestational tissues
• Many unanswered questions about optimal dosing and route of administration remain
• The only direct comparison favors vaginal progesterone
17 OHPC
The Bottom Line

• Screen all patients for history of SPTB
  – Live birth between 20 weeks 0 days and 36 weeks 6 days
  – Any type of delivery after spontaneous labor, PPROM, Abruption or Silent cervical dilation

• For previous deliveries between 20 -26 weeks
  – Consider prophylactic cerclage
• Progesterone therapy
  – 1st Line 17 OHPC
    • Dose is 250 mg im weekly
    • Start at 16 weeks if possible but still some affect as late as 24 weeks
    • Use Makena if possible but may use compounded if insurance issue or allergy documented
  – 2nd Line Vaginal Progesterone
    • Natural progesterone 200 mg suppository
    • Crinone gel 90 mg nightly
Progesterone Therapy
More Thoughts

• Oral progesterone not proven effective
  – Preliminary data available
• Less data and less convincing data about vaginal progesterone
• Offer progesterone if any previous delivery was spontaneous delivery between 16-20 weeks
• May still be some benefit even if treatment is started after 20 weeks
Progesterone Therapy and...

- Not for twins or triplets
- Not for women with symptomatic labor unless previous history of PTB
- Still offer 17 OHP even if last delivery was at term
- Progesterone and cervical shortening
  - Start treatment if not previously initiated
  - 17 OHP vs vaginal progesterone
The role of cerclage

Which patient and when
Role of Cerclage

• History of classic cervical insufficiency
  – Benefit from prophylactic cerclage
• Recent data suggests possible role in women with a history of sPTB
Vaginal US Cerclage Trial

• Prospective, randomized trial of cerclage to prevent recurrent sPTB

• 302 women randomized
  – Previous history of sPTB between 16 and 34 weeks gestation
  – Singleton pregnancy
  – Cervical length < 2.5 cm at < 23 weeks gestation

Primary Outcome
PTB < 35 weeks Gestation

Cerclage

No Cerclage

P=0.09

Odds ratio 0.67, 95% CI, 0.42 to 1.07
Cervical Length and Cerclage

• < 1.5 cm on initial exam
  – odds ratio = 0.23; 95% CI 0.08 to 0.66; p = 0.006
• Initial cervical length 1.5-2.5 cm
  – odds ratio = 0.84, 95% CI, 0.49 to 1.4; p = 0.52
• No apparent benefit from progesterone
Cervical Length < 1.5 cm
Gestational Age < 24 weeks

Evaluation and treatment of short cervix

Cervical Length < 1.5 cm or visible membranes

- Tocometry
- Rule Out Contractions

  - Negative contractions
    - Offer Cerclage
    - Follow-up in 1-2 weeks

  - Positive contractions
    - Admit to hospital for active tocolysis with Indocin
    - Follow-up in 1-2 weeks

1.5 – 2.5 cm Cervical Length

- Follow-up in 1-2 weeks
- Initiate progesterone if not previously done
Gestational Age > 24 weeks

Evaluation and treatment of short cervix

Cervical Length 1.0-2.5 cm
- Tocometry
- Rule Out Contractions

Positive contractions +/- Cervical change
- Admit to hospital for active tocolysis with Indocin
- Treat with steroids if not done previously
- Reevaluate cervical length in 48 hours

< 1.0 cm Cervical Length
- Admit to hospital for active tocolysis with Indocin
- Treat with steroids if not done previously
- Reevaluate cervical length in 48 hours

Negative contractions
- Initiate progesterone if not already done
- Follow-up in 1-2 weeks
History of SPTB and Short Cervix

• Meta-analysis of 5 trials
• Women with a history of SPTB and short cervix (<2.5 cm) n=504
• Rate of PTB < 35 weeks
  – 28.4% (71/250) in the cerclage compared with 41.3% (105/254) in the no cerclage groups
  – (relative risk 0.70, 95% confidence interval 0.55–0.89)
• Cerclage also significantly reduced
  – PTB < 37, 32, 28, and 24 weeks of gestation.
  – Composite perinatal mortality and morbidity (15.6% in cerclage compared with 24.8% in no cerclage groups; relative risk 0.64, 95% confidence interval 0.45–0.91).

Berghella et al. Obstet Gynecol 2011; 117:663
Case 1

- Was not offered 17 OHPC or vaginal progesterone
- Did not receive prophylactic cerclage or serial cervical lengths
- Presented at 27 weeks gestation with advanced cervical dilation without painful contractions
- Delivered < 4 hours after arrival
Screen for risk

At first prenatal visit:
- Does the patient have a history of any preterm birth (PTB)?
- Confirm EDC
- Confirm singleton pregnancy

- **Yes**
  - Consider evaluation of cervical length at time of anatomic survey (Ultrasound)
  - Cervical length < 25 mm?
    - **Yes**
      - Start vaginal progesterone 200 mg per vagina QHS
      - May substitute Crinone Gel
    - **No**
      - Routine care

- **No**
  - **No**
    - Routine care
  - **Yes**
    - Cervical length < 15 mm?
      - **Yes**
        - Consider ultrasound indicated cerclage placement
        - Continue 17 P or switch to Vag P
      - **No**
        - Continue 17 P

- **Was PTB between 16 and 24 6/7 weeks?**
  - **Yes**
    - Consider prophylactic cerclage placement at 12-14 weeks
    - Start 17 P at 16-20 weeks gestation
  - **No**
    - No

- **Does the patient have**
  - A history of a spontaneous PTB?
    - Singleton live birth between 16 and 36 weeks gestation?
    - Includes presentation as labor, PPROM, or advanced cervical dilation
  - **Yes**
    - Was PTB between 16 and 24 6/7 weeks?
      - **Yes**
        - Consider prophylactic cerclage placement at 12-14 weeks
        - Start 17 P at 16-20 weeks gestation
      - **No**
        - Start 17 P at 16-20 weeks gestation
        - May start after 20 weeks if needed
        - Evaluate Cervical length by TVUS between 16 0/7 and 23 6/7 weeks
  - **No**
    - No
Conclusions

• Women with a previous sPTB have a recurrence risk of 30-40%
  – We should pay attention to them
• A personal risk assessment is possible
• Cervical length can be used to assess ongoing risk and direct treatment
  – First at 18-20 weeks – Consider cerclage if < 1.5
  – Second at 22 weeks – Consider cerclage if < 1.5
  – Final at 26-29 weeks – Direct therapy with activity modification, steroids and tocolyis
Conclusions

• Offer Progesterone to all patients with a history of sPTB
  – Start at 16-20 weeks
  – Add as treatment if cervix shortens

• Benefits of the Utah Prematurity Prevention Clinic
  – Organized, comprehensive, consistent approach
  – May reduce rate of PTB
  – Provides and avenue for research
Questions?

Criticisms?