Preterm Birth Prevention: The Progesterone Strategy

Brad Lucas, MD, MBA, FACOG
Chief Medical Officer
Buckeye Community Health Plan
PRETERM BIRTH

A public health crisis
Born Too Soon in the U.S.

• Leading cause of infant morbidity and mortality
• 11.5% of all births
  – 450,000 babies annually
• Significant racial disparities
  – 16.8%, Black
  – 11.7%, Hispanic
  – 10.5%, White
• 50% occur in low risk pregnancies
• 50% of all pregnancy costs

*Preterm birth is less than 37 completed weeks gestation*
Impact on Medicaid

- Medicaid pays for 45% of all births in the U.S.
  - Higher rate of preterm birth: 1 in 8 babies
  - 1.3 times as much spent on that one premature baby as on the remaining seven uncomplicated babies combined
  - Twice as many adverse outcomes

- NICU admissions among most expensive hospitalizations

- CHIP and other support services continue for many years
  - Estimated $6.4 billion Medicaid burden in medical costs alone for preterm infants in the first 7 years of life (2005 cohort)

“In Ohio, NICU babies represent 0.15% of the Medicaid population but account for 15% of the total Medicaid spend.”
EVIDENCE BASED INTERVENTION

Causes, risk factors, and patient management
Causes of Preterm Birth: A Complex, Multi-factorial Syndrome

- 70% spontaneous
  - Preterm premature rupture of the membranes (PPROM)
  - Preterm labor
    - Infection
    - Idiopathic contractions
    - Cervical dysfunction

- 30% medical decision to initiate delivery
  - Maternal indication
    - Hypertension
    - Diabetes
  - Fetal indication
    - Intrauterine growth restriction
Risk Factors

• Obstetric history
  – Prior spontaneous preterm birth
  – Prior low birth weight infant
  – Prior high risk pregnancy

• Obstetric complications
  – Premature cervical shortening
  – Other cervical insufficiency
  – Cervical cerclage
  – Vaginal bleeding
  – Cervical uterine anomalies

• Medical complications
  – Hypertension
  – Gestational diabetes
  – Renal or cardiac disease
  – Maternal or intra-amniotic infection
  – Fetal intrauterine growth restriction

• Multiple gestations

• Race
  – African American

• Maternal age < 18 or > 40 years

• Low BMI

• Genetic factors

• Lifestyle factors
  – Smoking
  – Alcohol or drug use
  – Lack of prenatal care

• Lack of prenatal care
**Society Guidelines:**

**Progesterone to Prevent Preterm Birth**

**SMFM**

**SMFM Clinical Guideline**

**ACOG**

**ACNM**

**Position Statement**

The American College of Nurse Midwives (ACNM) offers the following:

- **Society Guidelines:**

  - Progesterone to Prevent Preterm Birth

  **Background**

  Progesterone to Prevent Preterm Birth:

  - **SMFM**
  - **ACOG**
  - **ACNM**

  **ACNM**

  Prevention of Preterm Labor and Preterm Birth

  The American College of Nurse-Midwives (ACNM) offers:

  - Prevention of Preterm Labor and Preterm Birth

  **Position Statement**

  The American College of Nurse-Midwives (ACNM) offers the following:

  - Prevention of Preterm Labor and Preterm Birth

  **Background**

  Progesterone to Prevent Preterm Birth: a comprehensive review of evidence for clinical practice.
Evidence Based Use of Progesterone

**Singletons**

- 17-OHPC: history of spontaneous preterm birth
  - 2003
  - Cuts risk by 1/3
- Vaginal progesterone: prematurely short cervix
  - 2011
  - Cuts risk in 1/2

**Multiples**

- Progesterone **NOT** effective in preventing preterm birth
Two High Risk Groups, Two Proven Interventions

• **1st risk screening:** comprehensive obstetric history at first prenatal visit
  – Relative risk = 2x
  – Recurrent preterm birth accounts for 15% of all preterm birth
  – 17-OHCP injections cut risk by 1/3

• **2nd risk screening:** mid-pregnancy cervical length measurement
  – Relative risk = 10x
  – At least 40% of pregnancies will deliver before 32 weeks if the cervix shortens to 20 mm or less before 24 weeks
  – Vaginal progesterone cuts risk by 1/2

• Combined, these two risk screening strategies identify more than 50% of pregnancies destined to deliver ≤ 34 weeks
Prior Spontaneous Preterm Birth
ACOG/SMFM Recommendations

• INDICATION
  – Singleton with history of spontaneous preterm birth
  – Asymptomatic

• PROGESTERONE TREATMENT
  – 17-OHPC: 250 mg IM weekly
    • Makena
    • Compounded
  – From 16-20 weeks until 36 weeks
    • Efficacy demonstrated for initiation ≤ 27 weeks

• Additional surveillance and intervention
  – Serial cervical length measurements from 16 weeks to 24 weeks
    • Consider cerclage if cervical length shortens to less than 25 mm
Prematurely Short Cervix
ACOG/SMFM Recommendations

• **INDICATION**
  - Singleton without history of spontaneous preterm birth
  - Asymptomatic
  - Transvaginal ultrasound (TVU) diagnosis of premature cervical shortening
  - Cervical length ≤ 20 mm @ 18-24 weeks

• **PROGESTERONE TREATMENT**
  - Vaginal progesterone: 90 mg gel or 200 mg suppository daily
    • Crinone 8%
    • Prometrium (generic)
    • Compounded
  - From diagnosis to 36 weeks
CERVICAL LENGTH AND VAGINAL PROGESTERONE

New recommendations
The Cervix During Pregnancy

- Cervical shortening is the final common pathway to parturition
- Premature cervical shortening can be “silent” for weeks before onset of preterm labor or PPROM
- Long subclinical phase allows prediction and preventive treatment

Hassan et al, Ultrasound Ob Gyn 2011
Perinatal Research Branch, NICHD

- 32,091 asymptomatic patients
  -Singletons
  -84% no prior preterm birth

TVU screening for short cervix
- 19\textsuperscript{0/7} to 23\textsuperscript{6/7} weeks
- 2.3% prevalence CL 10-20 mm

- 465 patients with CL 10-20 mm randomized to vaginal progesterone (90 mg gel) or placebo
- 45% reduction in PTB < 33 weeks
- 50% reduction in PTB < 28 weeks
- 43% reduction in any neonatal morbidity or mortality event
- 61% reduction in respiratory distress syndrome
- No fetal or neonatal safety signal
Screening and Treatment is Cost Saving

• Need to treat for benefit ratios
  – Treat 11 to prevent 1 early preterm birth
  – Treat 14 to prevent 1 NICU admission

• For every 100,000 women screened
  – $19.5 million saved
  – 22 neonatal deaths or long-term neurologic deficits prevented
  – 735 Quality Adjusted Life Years gained

• $500-750 million potential annual net savings in U.S.
Identifying the Short Cervix

• Current practice
  – Treat only “incidentally” found short cervix

• Change in practice
  – Universal cervical length screening
  – Adds cervical length measurement at 18-24 weeks gestation

• Per ACOG/SMFM
  – Reasonable clinical practice to enable treatment
  – Cannot mandate given limited access to TVU
Transvaginal Ultrasound (TVU)

- Per ACOG/SMFM
  - Diagnostic exam for intervention
  - Proper technique, quality control, monitoring essential
  - Certification recommended (https://clear.perinatalquality.org/)

- Screening and diagnosis test in one step

- Feasible in most settings with high ultrasound capacity
  - Maternal-Fetal Medicine practices
  - Ultrasound centers: sonographers
  - Generalists’ offices with full time sonographers

- Add TVU cervical length at the fetal anatomy scan
  - Standard protocol for the facility
  - Standing order from referring physician
Transabdominal Ultrasound (TAU)

- Designed to image the baby
- Full bladder required for fetal anatomy scan often elongates and distorts cervix
- Per ACOG/SMFM
  - Not reliable nor reproducible as a screening method
  - Not sufficient evidence to suggest benefit or harm of TAU screening for progesterone or other intervention
Cervicometer

- Single use, disposable
- Identify patients for indicated TVU
  - Classic two step screening and diagnostic approach
  - Allows equitable access to screening where TVU screening is not feasible
- Screen at prenatal visit before the anatomy scan
  - Add order for TVU cervical length when necessary

Vaginal cervical length measurement during speculum exam
## Studies Evaluating Cervicometer to Predict a Short Cervix by TVU

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harbor UCLA 2007</td>
<td>189</td>
<td>88%</td>
<td>92%</td>
<td>93%</td>
<td>99%</td>
<td>&lt; 30mm</td>
</tr>
<tr>
<td>W. Australia 2011</td>
<td>253</td>
<td>84%</td>
<td>73%</td>
<td>25%</td>
<td>98%</td>
<td>&lt; 24mm</td>
</tr>
<tr>
<td>Perugia, Italy 2013</td>
<td>50</td>
<td>100%</td>
<td></td>
<td></td>
<td>100%</td>
<td>&lt; 30mm</td>
</tr>
<tr>
<td>Thomas Jefferson (Philadelphia) 2014</td>
<td>358</td>
<td>100%</td>
<td></td>
<td></td>
<td>100%</td>
<td>&lt; 30 mm</td>
</tr>
</tbody>
</table>
A COMPREHENSIVE PROGESTERONE STRATEGY

Buckeye Community Health Plan
Preterm Birth Prevention with Progesterone Therapy

Singleton Pregnancies*

No history of spontaneous preterm birth

Screening for Short Cervix
Transvaginal Ultrasound or CerviLenz
18-24 weeks

Choose an algorithm

If TVU measurement

TVU ≤ 20 mm
Vaginal progesterone
daily 200-mg suppository or
90-mg gel from
diagnosis of short cervix to
36 weeks

TVU 20-25 mm
Repeat TVU
before 24 weeks

TVU ≥ 25 mm
Continue routine care

If CerviLenz measurement

CerviLenz < 25 mm
Follow-up TVU
Before 24 weeks

TVU ≤ 20 mm
Vaginal progesterone
daily 200-mg suppository or
90-mg gel from
diagnosis of short cervix to
36 weeks

TVU > 20 mm
Continue routine care

CerviLenz ≥ 25 mm

History of spontaneous preterm birth

17P 250 mg IM weeks
from 16-20 weeks to 36 weeks*

Cervical Length Measurement
Transvaginal Ultrasound
16-24 weeks

TVU < 25 mm
Consider cerclage; continue 17P

TVU ≥ 25 mm
Continue 17P

*Currently, there are no recommended progesterone interventions for multiple gestations.


Buckeye Community Health Plan allows starting 17P up to 28 weeks gestation.