Progesterone Therapy for Preterm Birth Prevention

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NORTH CAROLINA
Preterm Birth Prevention
SYMPOSIUM
MAY 23, 2016 • CHAPEL HILL

UNC Center for Maternal & Infant Health

UNC SCHOOL OF MEDICINE

Community Care of North Carolina

Funding for this project is provided in part by The Duke Endowment

Learning Objectives

By the end of this session, participants will be able to:

- **Recognize benefits of screening patients for progesterone use**
- **Identify indications for 17P**
- **Identify indications for vaginal progesterone**
- **Identify indications for cerclage for short cervix**
- **Recognize controversial management areas**

17P = 17α-hydroxyprogesterone caproate

Funding for this project is provided in part by The Duke Endowment

Background

Preterm Birth: Why worry?

1) Very common (~ 450,000 infants/yr)
2) Very expensive (~ $26 billion/yr)*
3) #1 cause of infant deaths
4) Intervention can reduce the risk

* 2007 IOM (www.marchofdimes.org/mission/the-economic-and-societal-costs.aspx)

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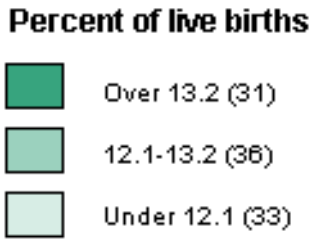
Preterm birth in North Carolina

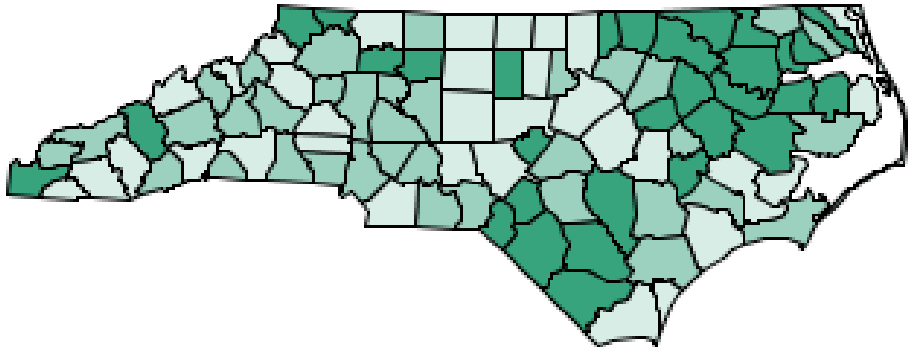
Infants born <37 weeks (12% of births)

- **13,410 infants**
  - **1:8 overall**
  - **1:6 African American infants**

Infants born <26 weeks

- **806 infants**





2010-2013 Average

National Center for Health Statistics, natality data.
Retrieved 9/29/15, from www.marchofdimes.org/peristats.

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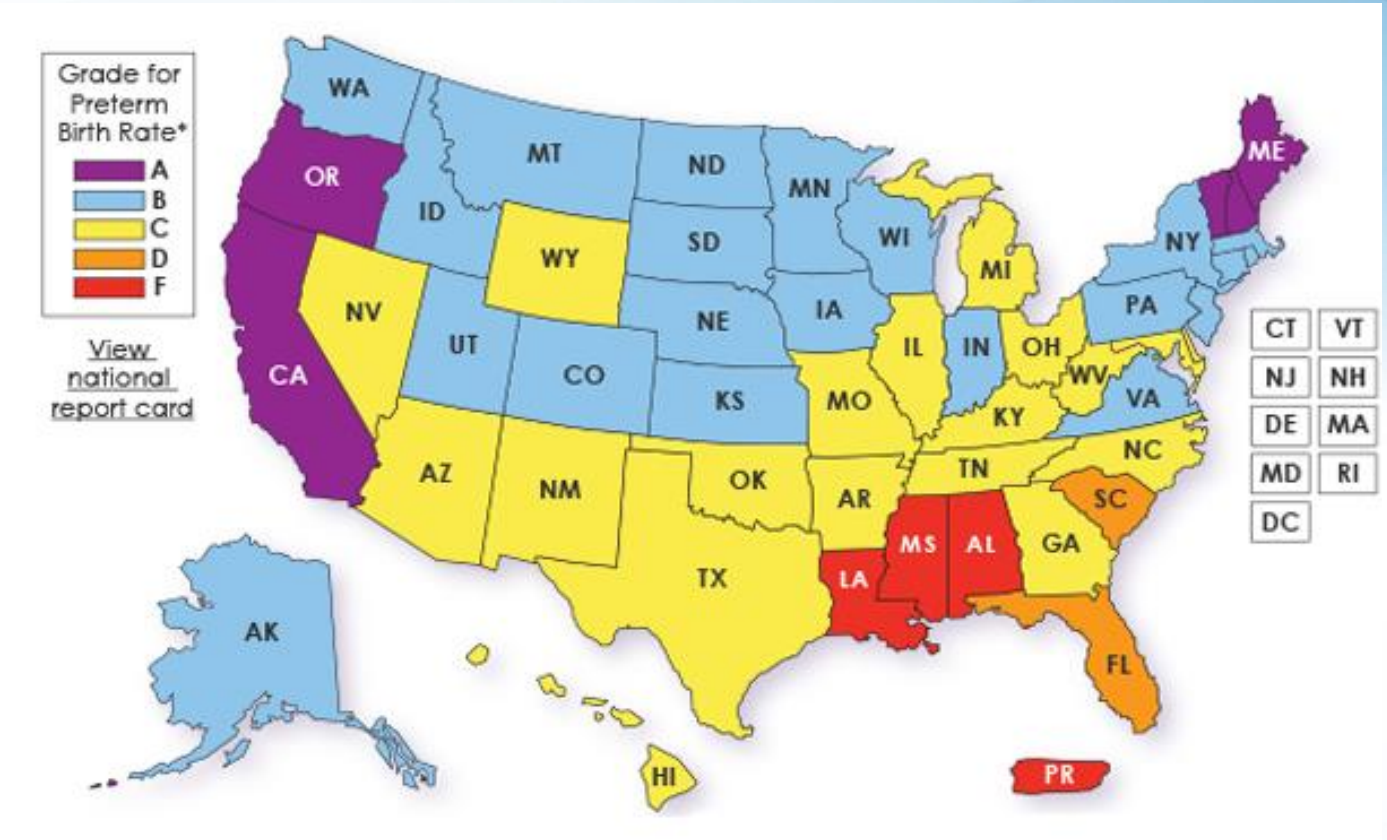
2014 March of Dimes Report Card



North Carolina	2006	2010	2014	2020 Goal
Preterm (< 37 weeks)	13.6%	12.7%	12.0%	9.6%

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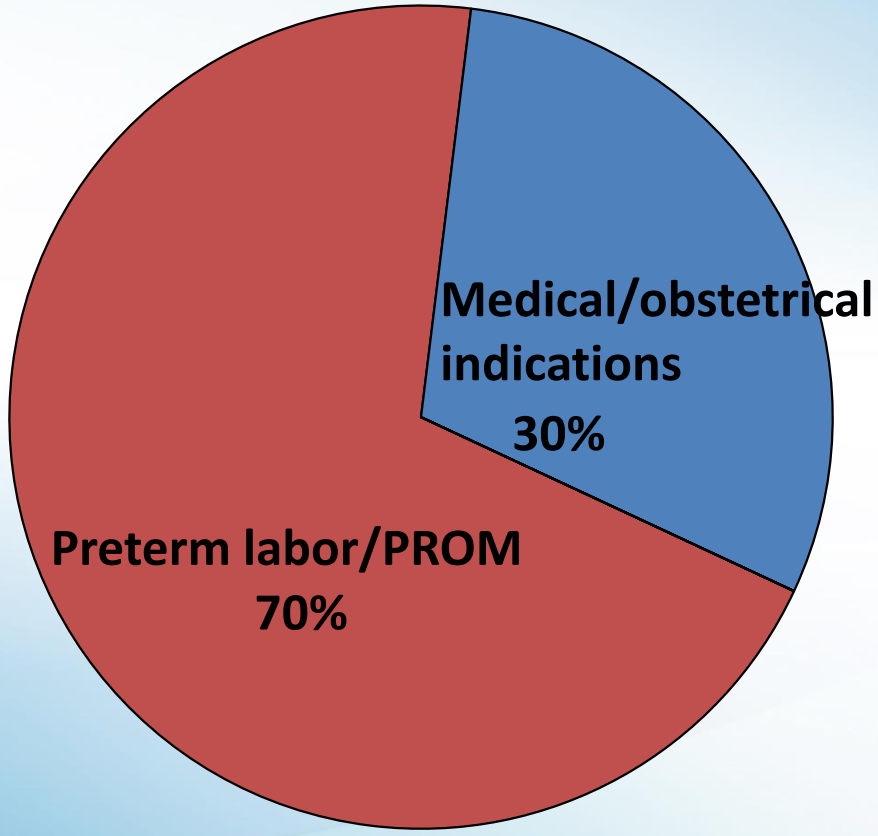
Preterm Birth: Etiology



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Recurrence Risks for Spontaneous Preterm Birth

	Risk of SPTB in next pregnancy
2nd pregnancy; 1st at term	9%
2nd pregnancy; 1st SPTB	22%
3rd pregnancy; 2 Prior SPTBs	42%
both < 32 weeks	57%
3rd pregnancy; 2 Term births	5%

Mercer (1999)

McManemy (2007)

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Progesterone Therapy

Two different preparations *with* two different indications

17P:

- prior spontaneous preterm birth

Vaginal progesterone:

- incidentally detected short cervix (ultrasound)

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17α-hydroxyprogesterone (17P)

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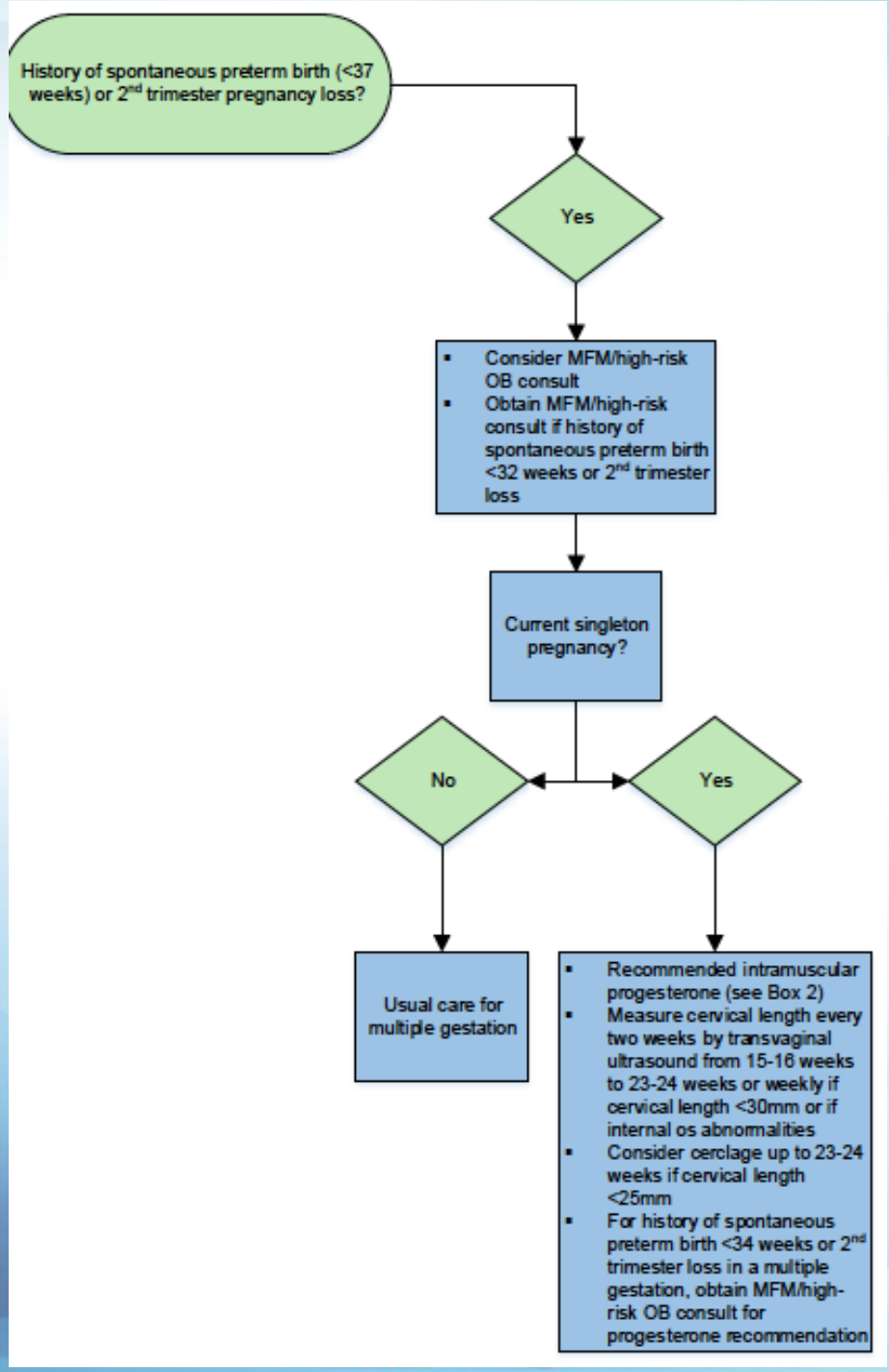
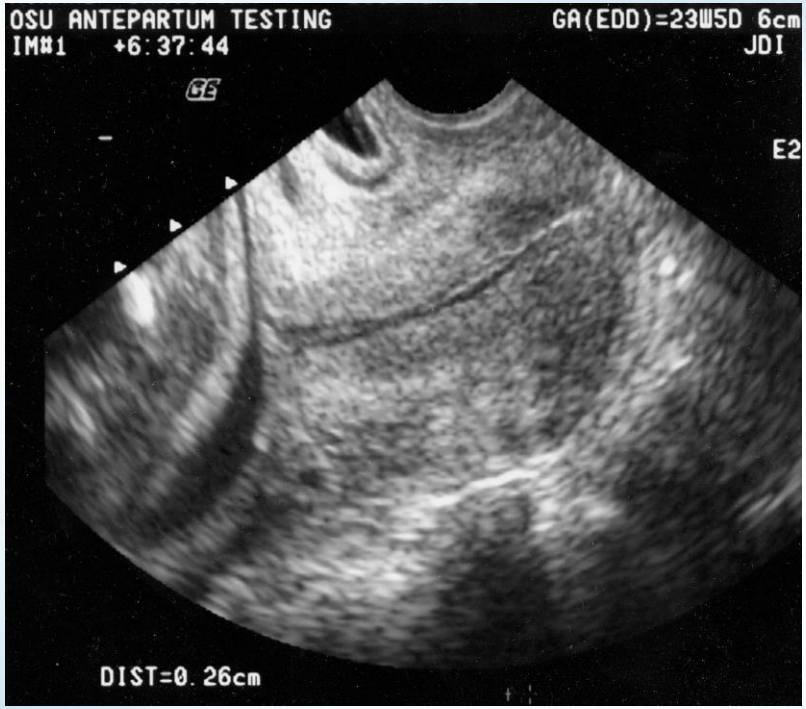
Prevention of sPTB



Preterm Birth History/ Cervical Length Screening Flowchart



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Evidence supporting 17P

NICHD randomized controlled trial (2003)

Eligible participants:

- **Prior spontaneous preterm birth 20^0 – 36^6**
- **Enrolled at 16-20 weeks**
- **Weekly 17P (250 mg) vs. placebo until 36 weeks**

Meis (2003)

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Evidence for 17P

Gestation	Placebo	17P	RR	P value
< 37 weeks	55%	36%	0.66	0.001
< 35 weeks	31%	21%	0.67	0.017
< 32 weeks	20%	11%	0.58	0.018

Approximately 33% reduction in preterm births

Meis (2003)

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ACOG Practice Bulletin 130 (2012)

Initial recommendation (2008)

Progesterone (17P) supplementation should be offered to women with a current singleton pregnancy and a prior spontaneous singleton preterm birth (start at 16-24 weeks)

Use in multiple gestations is not recommended

NC Pregnancy Medical Home (2011) requires PMH providers to offer and provide 17P to eligible patients

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17P Candidates and use

- Take a good history. Not indicated, if prior preterm birth was secondary to a medical or obstetrical indication.
- Previous singleton spontaneous preterm birth < 37 weeks
- Begin at 16-20 weeks and continue until 36 weeks
  - Start by 24 weeks at latest*
  - 250 mg IM weekly
- If dose is missed, resume therapy as soon as possible

*NC Medicaid will reimburse for 17p treatment for any patient with a history of spontaneous preterm birth regardless of weeks of gestation at initiation of therapy.

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Management dilemmas

- Prior SPTB of a twin gestation and now has a singleton
  - High-risk Ob consult
  - Consider 17P, if prior birth was “early” (i.e. < 30-32 weeks)
- Should 17P be continued, if a cerclage is done for a short cervix?
  - Yes
- Should 17P be used following tocolysis?
  - No, unless she was previously receiving it prior to tocolysis
- Should it be used in patients with risk factors for preterm birth, but no prior SPTB (multiples, uterine anomaly, + fFN, etc.)?
  - No

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Vaginal Progesterone

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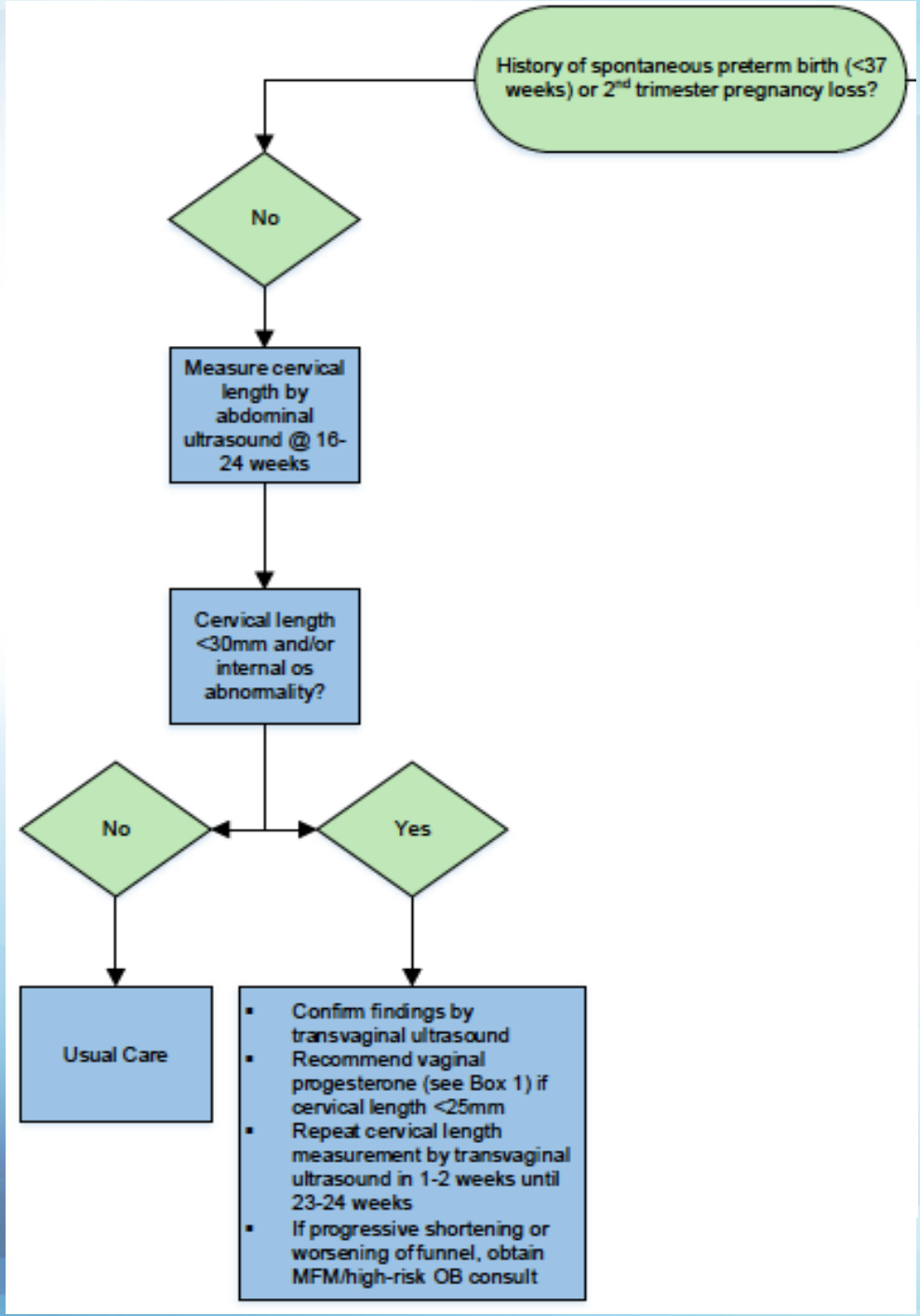
Prevention of sPTB

No Preterm Birth History/ Cervical Length Screening Flowchart



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Evidence for Vaginal Progesterone

Randomized controlled trial:

- **Asymptomatic women with cervix < 15 mm (20-25 wks)**
- **Vaginal progesterone (200 mg daily) vs. placebo**
- **24-34 weeks**

- **Delivery < 34 weeks**
  - **Progesterone: 19% (44% reduction)**
  - **Placebo: 34%**

Fonseca (2007)

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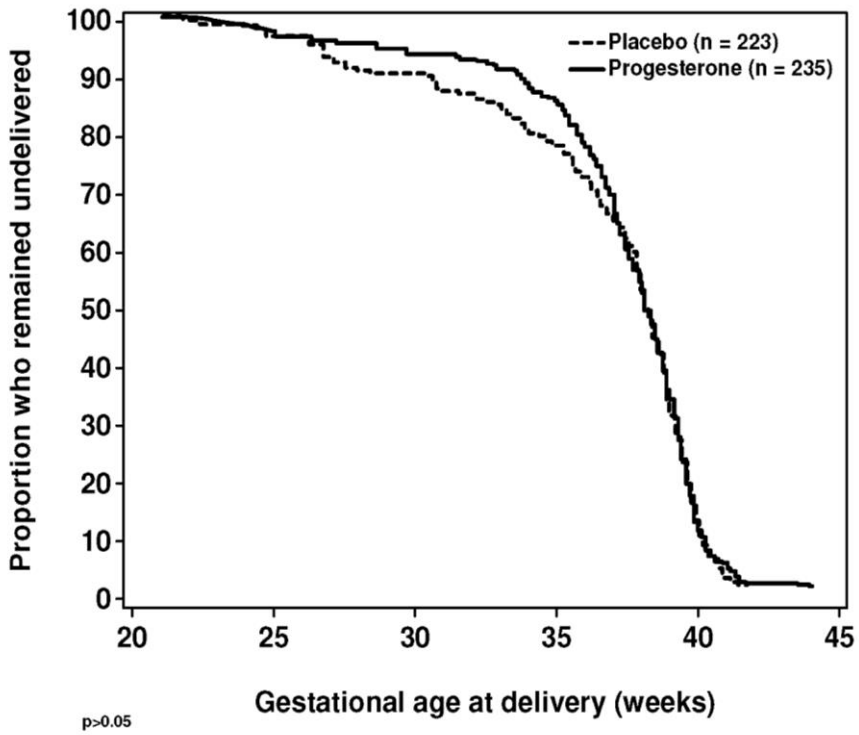
Evidence: Intervention for Short Cervix Effective

Vaginal progesterone (90mg gel)

- RCT n=32,091 screened, n=458 randomized
- High and low risk women with CL 10-20 mm
- Reduced risk by 45%

Figure 2A. Survival analysis of Intent-to-Treat Analysis Set – Proportion of Patients who remain undelivered according to treatment allocation (progesterone versus placebo)
This figure includes the Whole Population (patients with and without a prior history of preterm delivery)



Hassan, Ultrasound Obstet Gynecol 2011;38:18

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ACOG Committee Opinion 522 (2012)

Assess cervical length by transabdominal ultrasound at time of fetal anatomic survey. If cervix appears short (i.e. < 25-35 mm), perform transvaginal ultrasound

- (transabdominal cervical length for low-risk patients only)

Consider vaginal progesterone for asymptomatic women with a singleton gestation and no prior spontaneous preterm birth who have an incidental finding of short cervix (< 20 mm) before 24 weeks

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Assessing Cervical Length

Options for assessing Cervical Length include

- Digital Examination
  - Unable to see intraamniotic debris or choriodecidual separation
- Transabdominal Ultrasound
  - Factors that may affect reliability include obesity, fetal shadowing, and cervix position
- Transvaginal Ultrasound
  - Shown to be safe, reliable, and reproducible

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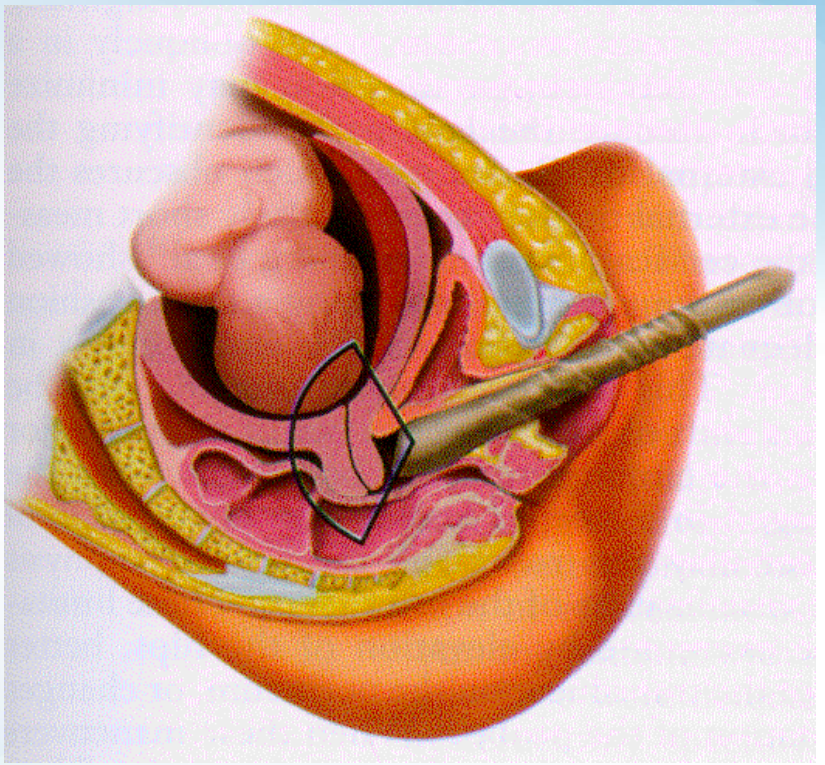
Training/Quality Control

Regardless of whether practitioners choose to screen universally or selectively, correct technique is critical to avoiding incorrect diagnosis and treatment.



Berghella, SMFM Publication Committee, Am J Obstet Gynecol 2012:10:1016

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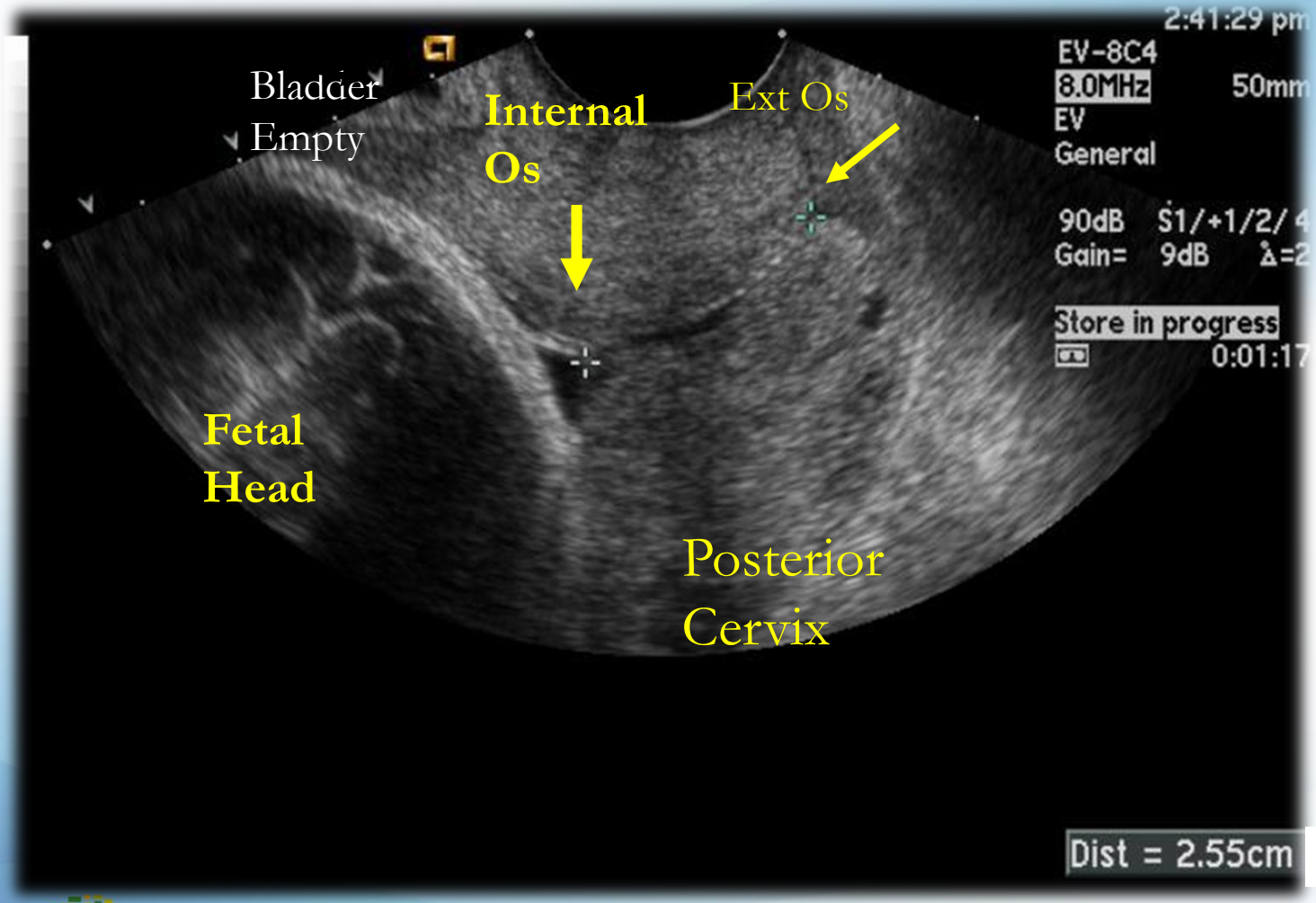
Normal Cervix



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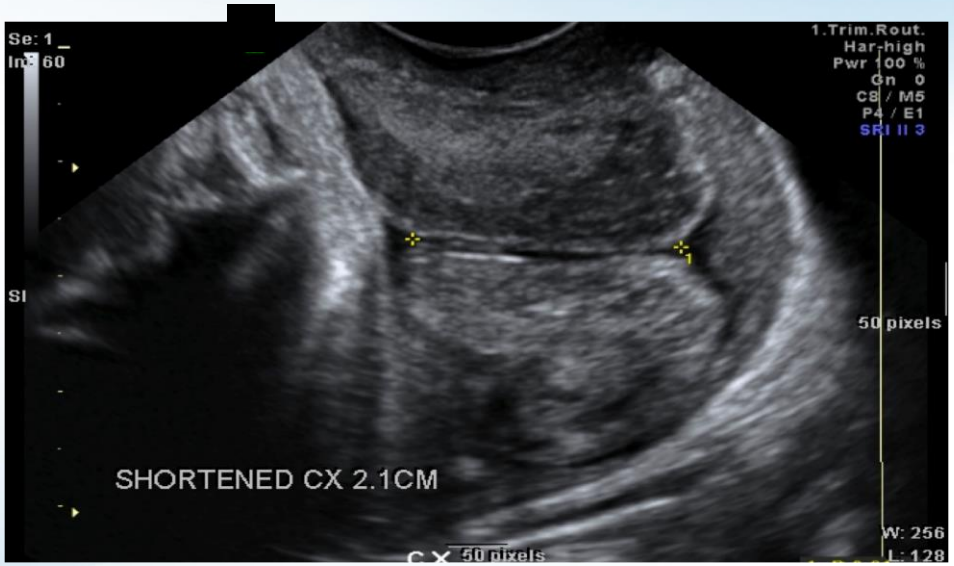
Cervical Screening Measurement Image Criteria

- Transvaginal Image
- Cervix ~ 75% of the image
- Anterior = Posterior Width
- Maternal Bladder Empty
- Internal Os Seen
- External Os Seen
- Cervical Canal Visible throughout
- Caliper Placement Correct
- Cervix Mobility Considered



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Dynamic Technique

- **Withdraw probe until blurred / Reapply**
- **Enlarge image (2/3 of screen)**
- **Measure Ext Os → Int Os along endo-cervical canal**
- **Apply fundal or suprapubic pressure**
- **Obtain 3 measurements, use shortest best**

cleaR
Cervical Length Education & Review

Berghella, Clin Obstet Gynecol 2003;46:947

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Other Factors Affecting Cervical Measurement

Gestational age:

- **Lower segment of uterus may be difficult to distinguish from cervix until somewhere between 16 and 20 weeks**
- **If can't tell at 16-18, ask her to come back at 18-20 wks**

Duration of scan – A scan < 3 minutes is inadequate

OPERATOR experience & training

- **Standardize method**

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Trans-Abdominal Pitfalls

- **Fetal parts may obscure cervix**
- **Bladder filling may elongate cervix and mask funnel**
- **Long distance from probe decreases resolution**
- **Manual pressure may compress lower uterine segment and mimic cervix**

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CLEAR Cervical Length Education & Review

CLEAR
Cervical Length Education & Review

- Cervical Length Education and Review Course
- Available online through the Perinatal Quality Foundation at

  https://clear.perinatalquality.org/

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Progesterone Formulations

17P

- **Makena®**
- **Compounded**

Vaginal progesterone

- **Prometrium® 200 mg (oral tablets, but use per vagina)**
- **Crinone® 90mg gel**
  - *** per vagina nightly**

Continue through 36th week of pregnancy

All of these preparations are covered by NC Medicaid; for more information or technical assistance, contact your local CCNC OB team.

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17P versus vaginal progesterone

- What if my patient can't/won't take 17P for the indication of prior sPTB?
  - Are 17P and vaginal progesterone equally effective & interchangeable?
  - Can I give her vaginal progesterone in lieu of 17P?
- Unfortunately this is unkown…

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Cerclage

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Prior SPTB and short cervix

Meta-analysis (5 studies)

- singleton gestation
- prior SPTB
- current cervical length < 25 mm before 24 weeks
- randomized to cerclage vs. no cerclage

- **Delivery < 35 weeks**
  - - cerclage: 28.4% RR: 0.70 (30% reduction)
  - - no cerclage: 41.3%

Berghella (2011)

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Multiple Gestation

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Twins and short cervix

- Cerclage
  - not recommended
  - associated with 2-fold increase in preterm births*

- Vaginal progesterone
  - no effect on preterm delivery rate
  - ACOG: not recommended
  - some experts recommend**:
    ~ 50% decreased risk of adverse perinatal outcome (RDS, IVH, NEC, sepsis, or neonatal death)

*Berghella (2005)
**Romero (2012)

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Summary

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Recommendations: Singleton gestation

Prior spontaneous preterm birth < 37 weeks

- consider high risk pregnancy consultation
- weekly 17P from 16-36 weeks

Prior spontaneous preterm birth < 32 weeks

- obtain high-risk pregnancy consultation
- weekly 17P from 16-36 weeks
- TV cervical length every 2 weeks from 15-23 weeks
- if cervix is 25-29 mm, assess weekly
  - consider cerclage, if cervix is < 25 mm

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Recommendations:
Singleton gestation

No prior spontaneous preterm births

- **transabdominal cervical length at anatomy scan (18-24 wks)**
- **if cervix is < 30-35 mm, perform transvaginal ultrasound**
- **if cervix is < 25 mm by transvaginal ultrasound:**
  - **vaginal progesterone**
    - **200mg tablets (Prometrium®) nightly**
    - **90mg gel(Crinone®) nightly**

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Recommendations:
Multiple gestation (DFZ)

Prior SPTB:

- consider 17P

Short cervix:

- no cerclage (doubles risk for preterm delivery)
- consider vaginal progesterone

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Grand Summary

Current pregnancy	Past SPTB	Recommendation
Singleton	Singleton	17P; cerclage (if cervix < 25 mm, 16-23 wks)
Singleton	Multiple	unclear; consider 17P
Singleton	No	not 17P candidate vaginal progesterone if cervix < 25 mm
Multiple	Singleton	unclear; consider 17P
Multiple	Multiple	unclear
Multiple	No	not 17P candidate
Multiple	-------	cervix < 25 mm: NO cerclage consider vaginal progest

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References

- **Berghella et al. Obstet Gynecol 2005;106:181-9.**
- **Berghella et al. Obstet Gynecol 2010;117:663-71.**
- **Fonseca et al. NEJM 2007;357:642-9.**
- **McManemy et al. Am J Obstet Gynecol 2007;196:576.**
- **Meis et al. NEJM 2003;348:2379-85**
- **Mercer et al. Am J Obstet Gynecol 1999;181:1216.**
- **Romero et al. Am J Obstet Gynecol 2012;206:124.e1-19.**

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References

- **ACOG:**
  - **Prediction and prevention of preterm birth. Practice Bulletin No. 130. October 2012**
  - **Incidentally detected short cervical length. Committee Opinion N. 522. April 2012**
  - **Cerclage for the management of cervical insufficiency. Practice Bulletin No. 142. February 2014**

- **www.marchofdimes.org**

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Questions and Comments?

Thank you.

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