

Current Status and Clinical Utility of Cervical Assessment

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Spontaneous Preterm Birth (SPTB):

Assumptions:

- #1. Spontaneous preterm birth has a significant impact on the health and well being of the infant, the family, the health care system and the society.
- #2. Identifying women at increased risk of spontaneous preterm birth allows for targeted therapy to prevent the preterm birth and its consequences.

SPTB: The Impact

- Incidence ~5-11% of all pregnancies (3-7% @ <34w GA)
 - Ireland 4.5%
 - United States 12.7%
 - **Canada 7.6%**
- 70% morbidity/mortality not associated with anomalies
- 40x risk death in 1st year
- short term: BPD, IVH, ROP, infection
- longterm:
 - 1/2 children with CP
 - 1/3 children with abn vision
 - 1/4 children with chronic lung disease
 - 1/5 children with MR

SPTB: The Impact

Morbidity persists to adulthood:

- increased incidence behavioral problems
- low birth weight linked to CAD

Hospital Cost

\$ 9700 per NICU stay

\$ 117 000 if BW <750g

4% operating expenses

Recurrence Risk

- 2.0 fold
- up to 40% risk if > 2 prior SPTB

What tools can we use to predict SPTB?

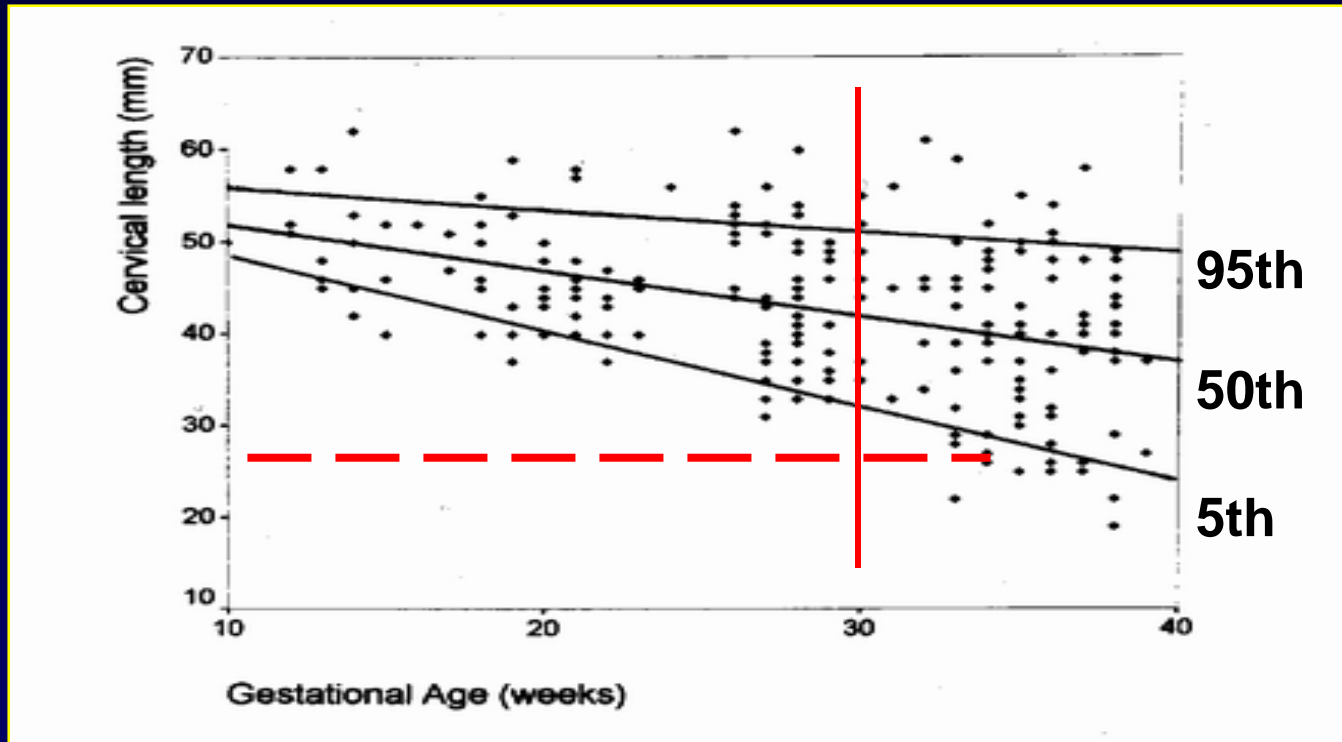
SPTB: Cervical Assessment

Role of the cervix through gestation:

1. Act as barrier to delivery of the infant: load bearing strength
 - structure: ECM: collagen type I and III
proteoglycan
elastin
Cellular: epithelium (glands)
fibroblast
vessel
 - increase cellular content by 50%
2. Act as barrier to ascending infection: immune function
 - gland cells: immune cell surface markers
 - mucus, NK like cells

Transvaginal Sonographic Cervical Length Changes During Normal Pregnancy

Gramellini et al; J Ultrasound Med (2002)



Non-pregnant:

3.1-3.8 cm

First Trimester:

4.6 -5.2 cm

Same pattern:

nulliparous and multiparous

SPTB: Cervical Assessment

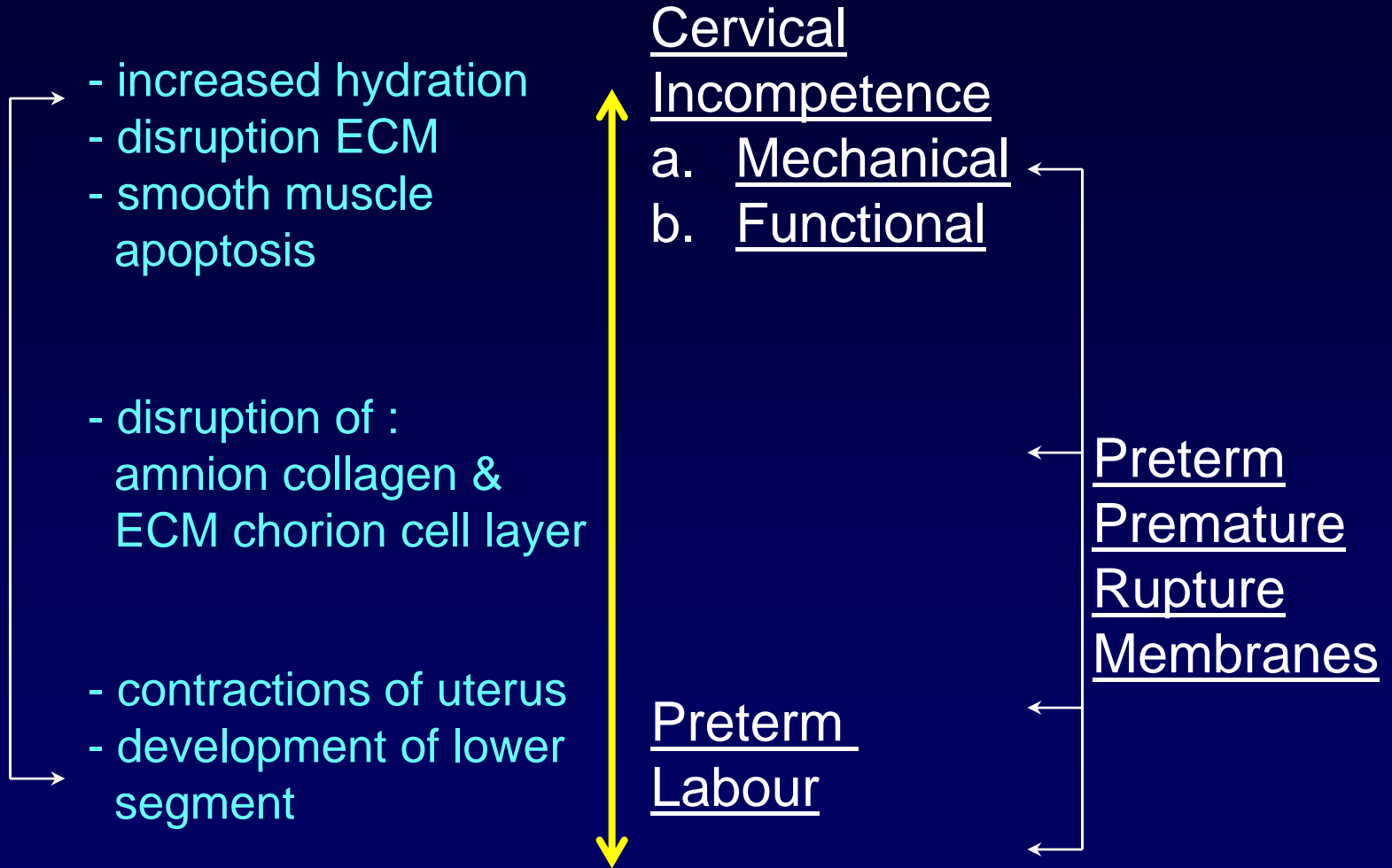
Role of the cervix @ end of gestation: efface / dilate

- breakdown ECM
- smooth muscle apoptosis
- increase H₂O content
- dilatation under pressure

If a cervix prematurely effaces and/or shortens then the cervix has become an anatomic marker of a pathological process

SPTB: Why use cervical length ?

MMP
Cytokine
PG



Can cervical length predict SPTB ?

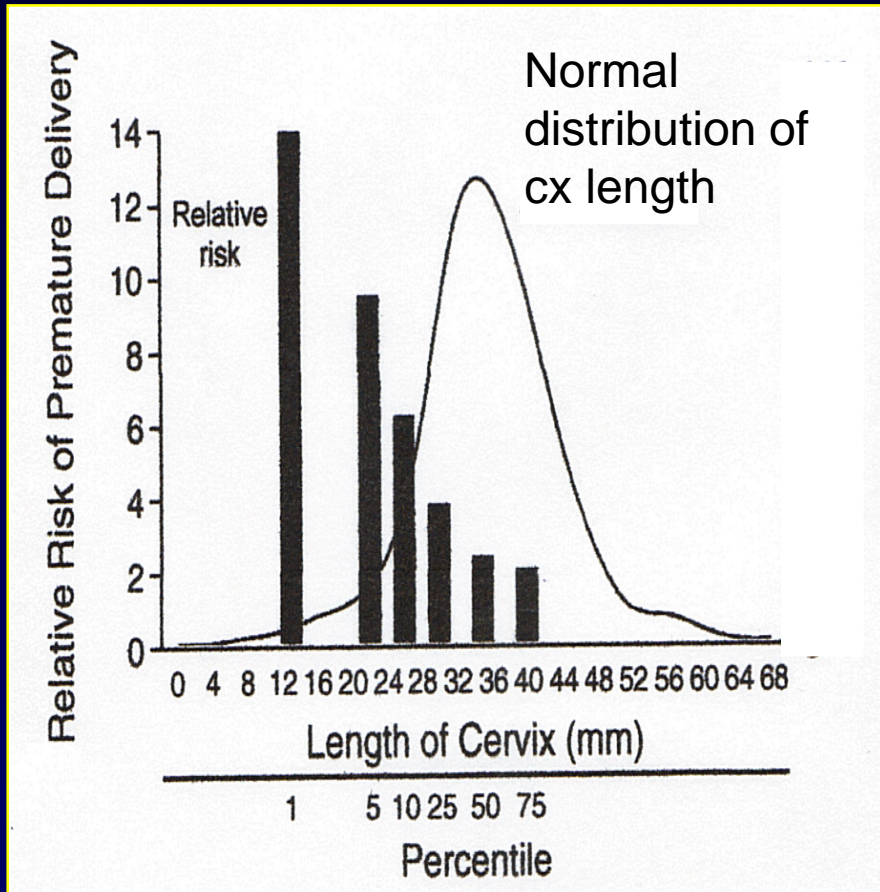
Question: Can the length of the cervix measured at 24 and 28w predict SPTB < 35w ?

Method: Multicentre, prospective study
Asymptomatic general population
2915 subjects at 24w
2531 subjects at 28w (delivered, lost)

Results:

- SPTB was indirectly correlated with cx length
- Significant at both 24 and 28w

Compared with the 75th percentile of length (4 cm)



Cx Length	RR
≤ 4 cm (75 th percentile)	1.98
≤ 3.5 cm (50 th percentile)	2.35
≤ 3.0 cm (25 th percentile)	3.79
≤ 2.6 cm (10 th percentile)	6.49
≤ 2.2 cm (5 th percentile)	9.49
≤ 1.3 cm (1 st percentile)	13.99

Baseline risk 7.6% x 6.49 RR (<10th percentile) = 46.7% SPTB

Accuracy of cervical transvaginal sonography predicting preterm birth : a systematic review

Honest et al, Ultrasound Obstet Gynecol 2003.

Goal: Obtain valid and reliable accuracy estimates of TVUS in predicting SPTB

Method: Systematic review

Criteria: asymptomatic / symptomatic
general population
known GA at birth
observational cohort

46 studies 31 577 women

Results: Odds ratio for SPTB varies:

- GA at assessment
- Cut off for PTB (< 32w, <34w, <37w)

Summary: Cervical Length and SPTB

Singleton Asymptomatic Patient PTB < 34 weeks

@ < 20 weeks gestation:

	< 25 mm LR was 6.29 (x 7.6% = 47.8%)	5 studies
**	< 15 mm LR was <u>30</u> (x 7.6% = > 100%)	1 study
	> 25 mm neg LR was 0.75	

@ 20-24 weeks gestation:

	< 25 mm LR was 4.4 (x 7.6% = 33.4%)	3 studies
**	< 15 mm LR was <u>27.9</u> (x 7.6 = > 100%)	1 study
	> 25 mm neg LR was 0.4 (x 7.6% = 3.0%)	

Summary: Cervical Length and SPTB

Singleton Asymptomatic Patient
PTB < 34 weeks

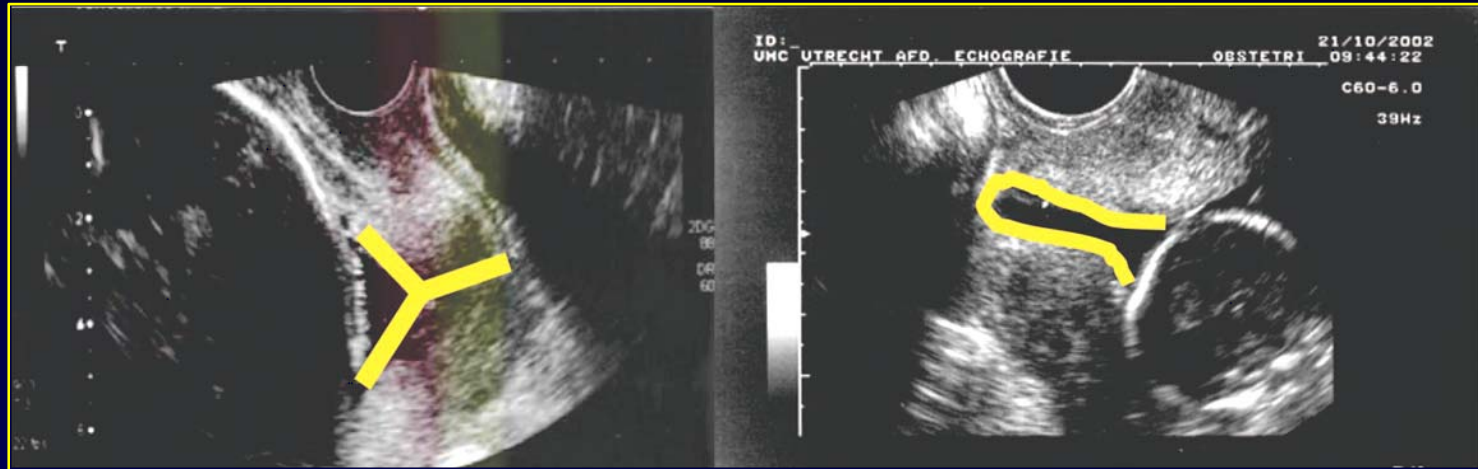
@ > 24 weeks gestation:

< 25 mm LR was 4.0 (x 7.6% = 33.0%) 4 studies

< 15 mm LR was 7.9 (x 7.6 = 60.0%) 1 study

> 25 mm neg LR was 0.62 (risk reduced by 62% to 2.9%)

SPTB: The Role of Cervix Funneling



Controversies in Measuring the Funnel:

- ? Independent or dependent of cx length
- ? Which measurement:
 - presence or absence
 - funnel width
 - funnel length
 - funnel shape
 - % of the total cervical length
 - canal width

Cervical length and funneling at 23 weeks of gestation in the prediction of spontaneous early preterm delivery

To et al, *Ultrasound Obstet Gynecol*; 2001

Goal: to determine the possible additional risk of SPTB if funneling is present

Method: 6819 singleton pregnancies
22-24 weeks
screening test for PTB

Results: 4% pregnancies have funnel present
98% if length ≤ 1.5 cm
25% if length 1.6-3.0 cm
1% if length > 3.0 cm

6.9% PTB LR 1.8

Presence of
funnel did not
improve LR

Does the presence of a funnel increase the risk of adverse perinatal outcome in a patient with a short cervix?

Rust et al, AJOG; 2005.

Goal: to determine whether the presence of a funnel alters the outcome of patients with a short cervix

Method: singleton pregnancies
 ≤ 2.5 cm +/- funnel (n=82)

Results:

- presence of funnel had increase incidence of:
 - PTL
 - abruptio
 - PPROM
 - neonatal mortality / morbidity
- size did not correlate with rate of PTB
- as a categorical variable – correlated with SPTB

SPTB: Consensus Role of Cx Length & Funnel

In the asymptomatic general population:

- Cut off of <10thtile (2.5cm) best predictive values at each GA
- Funnel best used as a categorical variable: present / absent
- Predictive value appears to be related to length: not strictly additive

SPTB: The Effect of Fundal Pressure

Goal of fundal pressure: to elicit cervical shortening and funneling to unmask cervical incompetence
“test of competence”

Response to fundal pressure: decrease in cx length with 15 sec fundal pressure

2 Studies:

Guzman et al, 1994 (n=181)

- A larger portion of patients who had + response to FP (n=31) delivered preterm compared with no response (n=150) {6% vrs 50%}

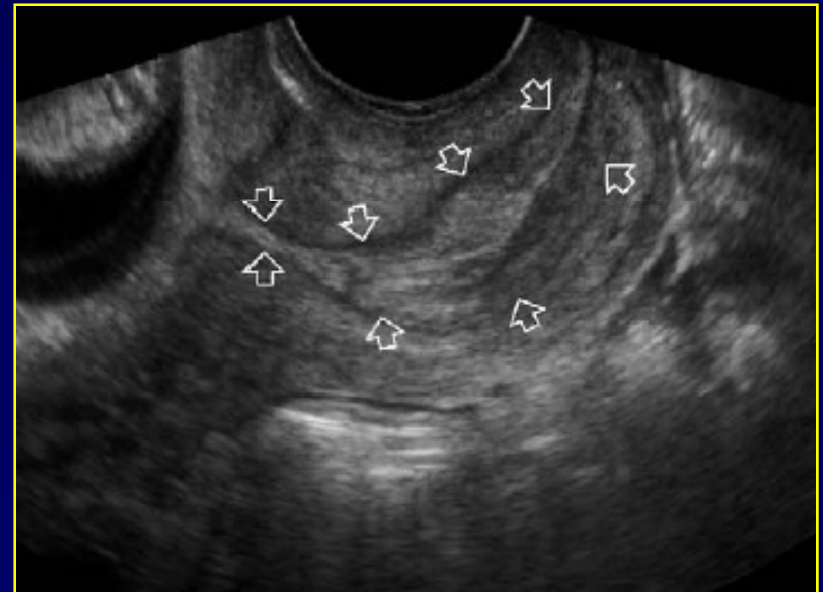
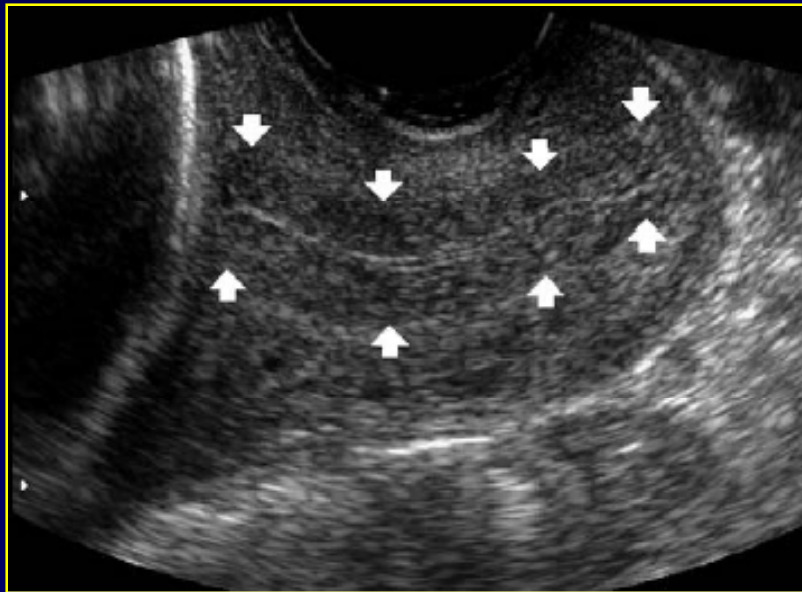
Guzman et al, 1997 (n=10)

- + FP response identified a cx that underwent subsequent shortening

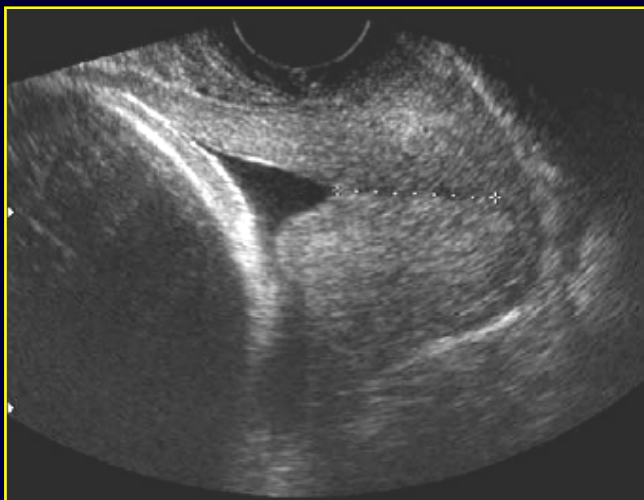
SPTB: The Effect of Gland Area



? Does the absence of the gland area predict PTB



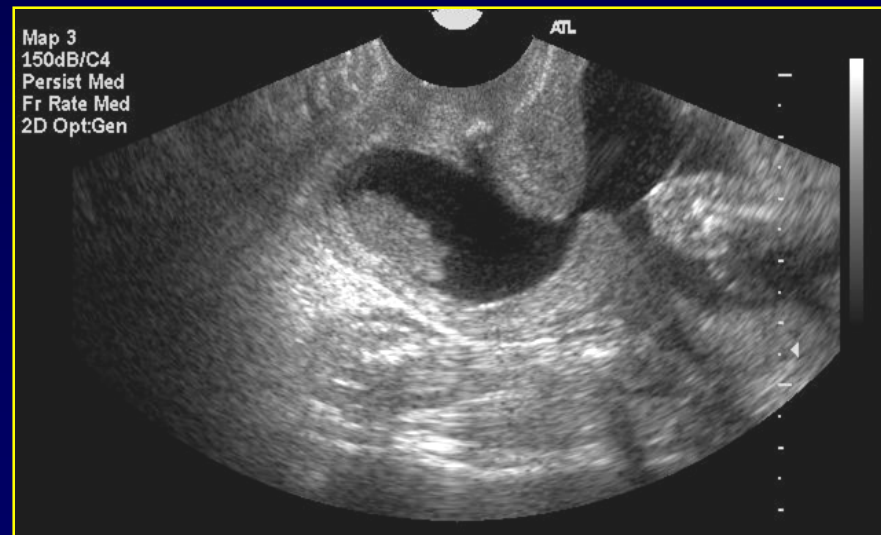
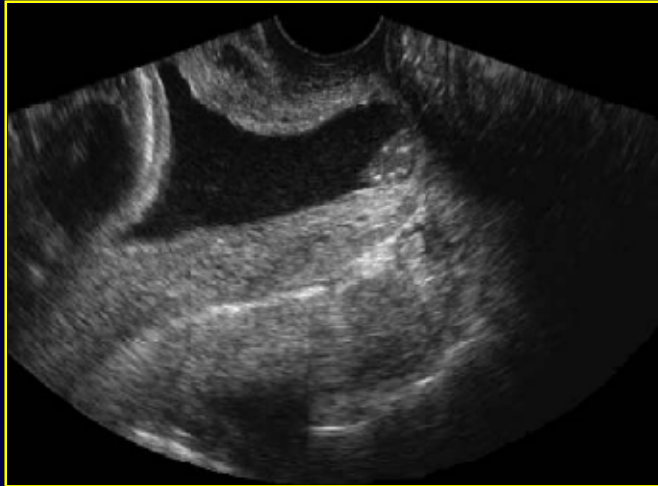
Other Cervical Characteristics: Gland Area



Ultrasonographic parameters	Category	n (%)	Sens (%)	Spec (%)	PPV (%)	NPV (%)	p (x ²)	OR crude	OR adj (p)
Cervical length	<20 mm	4	18.0	98.1	40.0	94.8	<0.001	12.2	2.1 (0.664)
	≥20 mm	17						1.0	1.0
Cervical funneling	Present	3	14.3	96.5	21.4	94.4	0.016	4.6	0.6 (0.745)
	Absent	18						1.0	1.0
Cervical gland area	Absent	8	38.1	99.7	88.9	96.0	<0.001	194.5	175.1(<0.001)
	Present	13						1.0	1.0
	Total	21							

Caution: subjective measure
 small study
 contradicts Sekiya et al (1998)

SPTB: The Effect of Debris / Sludge



? What is the prevalence and significance of sludge

Sludge present: 1% all pregnancies

<i>Outcome variable</i>	OR	95% CI	P
Positive amniotic fluid cultures	19.2	1.14–332	0.04*
Histological chorioamnionitis	8.3	1.3–50.9	0.02*
Admission to NICU	2.9	0.5–16.8	NS
Composite neonatal morbidity	0.85	0.16–4.6	NS
Perinatal death	3.3	0.3–40.5	NS
Spontaneous delivery			
Within 48 h	19.6	1.5–257.4	0.02*
Within 7 days	11.7	1.7–81.6	0.01*

Conclusion: sludge associated with PTB < 34w
and risk of chorioamnionitis

The Dynamic Cervix

Dynamic cervical change: real time shortening of the cervix

Question: Is the dynamic cervix predictive of PTB ?

Known Cx Incompetence

15/56 patients: cx opened spontaneously on TVUS exam

Asymptomatic Women

Dynamic change (+/- 3.4 mm) present in 9% of patients

? Unknown effect on risk of PTB

Symptomatic Women

Dynamic change (+/- 7.1 mm) present in 48% of patients

Usually occurred during a contraction

Minimal cx length and **NOT** dynamic change was predictive of PTB

Cervical Length Measurements and Special Circumstances

1. High risk patient (previous PTB; symptomatic)
2. In combination with FFN
3. Absolute length versus rate of change of length
4. Multiple gestation
5. Cervical length and cerclage
6. Cervical length and uterine anomalies
7. Cervical length and cervical surgery
8. Cervical length post fetal therapies
9. Cervical length and PPRM
10. Cervical length and polyhydramnios

Gestational age at cervical length measurement and incidence of preterm birth

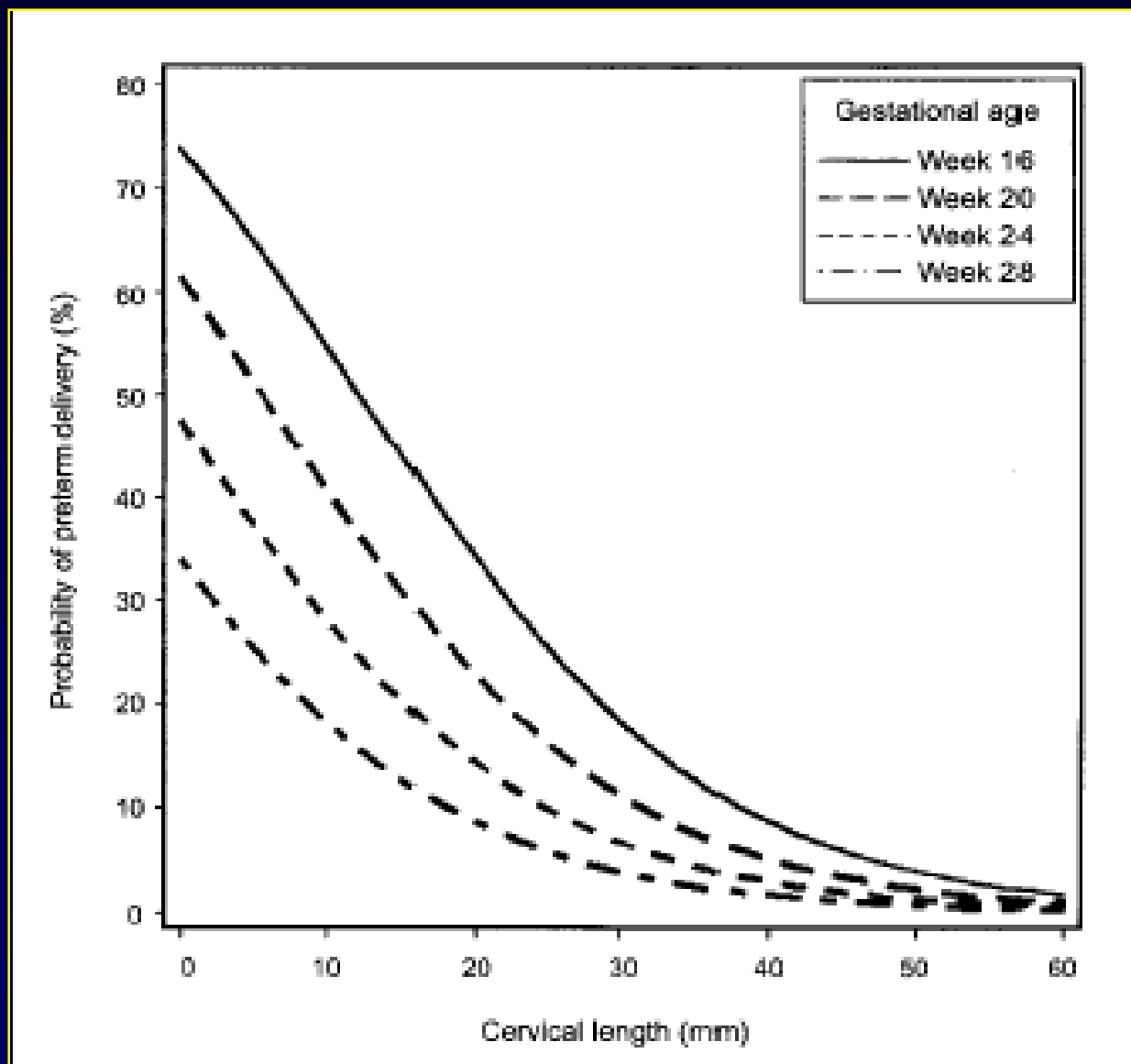
Berghella et al, Obstet Gynecol; 2007.

Rationale: GA at measurement and OBHx affect predictive value of TVUS cx length

Goal: estimate the risk of SPTB by TVUS and gestational age at which cervical length was measured

Method: retrospective n= 750
measurements from 16-28w
singleton
cerclage excluded
inclusion criteria: Hx PTB
cone biopsy
uterine anomaly
>2 D&E

Risk of PTB < 32 per week of gestation and mm of cervix



Risk PTB

↓ 5.5% per week

↓ 6.0% per mm

Table 2. Predicted Probability of Preterm Delivery Before Week 35, by Cervical Length (mm) and Time of Measurement (Week of Pregnancy)

Cervical Length (mm)	Week of Pregnancy													
	15	16	17	18	19	20	21	22	23	24	25	26	27	28
0	69.8	68.7	67.5	66.3	65.2	64.0	62.7	61.5	60.2	59.0	57.7	56.4	55.1	53.8
5	62.5	61.3	60.0	58.7	57.5	56.2	54.9	53.6	52.2	50.9	49.6	48.3	47.0	45.7
10	54.6	53.3	52.0	50.7	49.4	48.1	46.7	45.4	44.1	42.8	41.6	40.3	39.0	37.8
15	46.5	45.2	43.9	42.6	41.3	40.1	38.8	37.6	36.3	35.1	33.9	32.8	31.6	30.5
20	38.6	37.3	36.1	34.9	33.7	32.5	31.4	30.3	29.2	28.1	27.0	26.0	25.0	24.0
25	31.2	30.1	29.0	27.9	26.9	25.8	24.8	23.9	22.9	22.0	21.1	20.3	19.4	18.6
30	24.7	23.7	22.8	21.8	21.0	20.1	19.3	18.5	17.7	16.9	16.2	15.5	14.8	14.2
35	19.1	18.3	17.5	16.8	16.1	15.4	14.7	14.1	13.4	12.8	12.2	11.7	11.2	10.6
40	14.6	13.9	13.3	12.7	12.1	11.6	11.1	10.6	10.1	9.6	9.2	8.7	8.3	7.9
45	11.0	10.5	10.0	9.6	9.1	8.7	8.3	7.9	7.5	7.2	6.8	6.5	6.2	5.9
50	8.2	7.8	7.4	7.1	6.7	6.4	6.1	5.8	5.5	5.2	5.0	4.7	4.5	4.3
55	6.0	5.7	5.5	5.2	4.9	4.7	4.5	4.3	4.0	3.8	3.7	3.5	3.3	3.1
60	4.4	4.2	4.0	3.8	3.6	3.4	3.3	3.1	3.0	2.8	2.7	2.5	2.4	2.3

- * Risk of recurrent SPTB varies with: GA at measure
Total length of cx
- * Not affected by: # or GA of prior PTB
- * >28w GA - cx shortens- this is not correlated with SPTB

Cervical Length and Maternal Characteristics

Goal: to create a model to calculate specific PTB risk based on combining maternal factors and cervical length

Methods: TVUS cervical length at 22-24⁺⁶w
maternal demographics: age
ethnicity
BMI
smoking
Hx cx surgery
OB Hx

n= 39 284 pregnancies

Results: #1 predictor cervical length
improved by OB Hx, maternal characteristics

Cervical Length and Maternal Characteristics

Model Prediction of PTB <32w:

Set with a 5% false + rate

Factors	Detection Rate
Maternal Factors (age + OBHx)	29%
Cervical Length	48%
Combination of both	57%

Cervical length can be used in combination with maternal factors to better predict risk of PTB

SPTB: Effect of symptoms and cx length

Singleton Symptomatic Patient

PTB < 34 weeks

Very little data

@ 20-24 weeks gestation: (2 studies- only 30 mm cutoff)

< 30 mm LR was 1.98
> 30 mm neg LR was 0.28

Honest et al, Ultrasound Obstet Gynecol (2003)

@ 24-28 weeks gestation: <25 mm

<35w LR 2.05 PPV 24 NPV 94
<7d LR 2.25 PPV 36 NPV 94

Schmitz et al, AJOG (2003)

Cx Length and Fetal Fibronectin

Rationale:

- 23% of symptomatic patients with a + FFN delivered within 7d of the test compared with 2% with a - FFN

Question: Does the combination of short cervix and + FNN provide better prediction than each test alone

In both asymptomatic and symptomatic (PTL) positive FFN did not improve the predictive value of the cx length measurement alone

WHY ?

FFN positivity increases as cervical length decreases

Heath et al, BJOG; 2000

Tsoi et al, Ultrasound Obstet Gynecol; 2006.

Selective use of fetal fibronectin detection after cervical length measurement to predict spontaneous preterm delivery in women with preterm labor

Schmitz et al, AJOG; 2006.

Goal: to determine whether selective use of FFN after TVUS cervical length predicts SPTB in symptomatic patients better than either indicator alone

Method: TVUS then FFN for all women
n=359

Results: 13.4% PTB <35w
6.3% PTB within 7d

Table II Predictive values for preterm birth of cervical length, fetal fibronectin, and selective use of fetal fibronectin in ultrasonography-selected patients (n = 359)

Predictors	Se (%) (95% CI)	Sp (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)
Delivery <35 wk*						
CL ≤25 mm	75 (60-86)	63 (58-69)	24 (17-32)	94 (90-97)	2.05 (1.64-2.55)	0.40 (0.24-0.65)
fFn ≥50 ng/mL	63 [†] (47-76)	81** (76-85)	33 (24-44)	93 (90-96)	3.24 (2.36-4.44)	0.46 (0.32-0.67)
Selective test	67 [§] (52-80)	81** (77-86)	36 (26-46)	94 (91-97)	3.57 (2.63-4.86)	0.41 (0.27-0.61)
Delivery <7 d[†]						
CL ≤25 mm	87 (66-97)	61 (56-67)	13 (8-20)	99 (96-100)	2.25 (1.83-2.77)	0.21 (0.07-0.61)
fFn ≥50 ng/mL	83 [¶] (61-95)	79** (74-83)	21 (13-31)	99 (96-100)	3.91 (2.96-5.17)	0.22 (0.09-0.54)
Selective test	83 [¶] (61-95)	79** (74-83)	21 (13-31)	99 (96-100)	3.91 (2.96-5.17)	0.22 (0.09-0.54)

359 patients presented → 159 patients Cx < 30 mm

- FFN added to Cx length no better than FFN alone
- FFN after Cx length decreased # FFN tests by 200 (55%)

The Rate of Change of Cervical Length



High risk patients based on OBHx with stable cervical length and proceeded to a mean GA 37 ± 3 w

Naim et al (2002): Unselected women (n=193)

- If decreased 10 mm/month - OR for PTB <32w 6.8

Owen et al (2001): In high risk women

- Term patients shortened cx by 1.0 mm /wk
- PTB patients shortened cx by 2.5 mm /wk
- if cx shortening & length <2.5cm: RR of 4.5

Early rate of change may be a better predictor of PTB as compared with a single cx length measurement

Effect of shortening observed up to 28 w

Multiple Gestation and Cervical Length

Twin Gestation:

@ 22w gestation:

Both length < 25 mm and presence of funneling predict PTB

@ 27w gestation

Length < 25 mm predicts PTB

** Likelihood Ratio of PTB for cx length < 25 mm: **5.4**

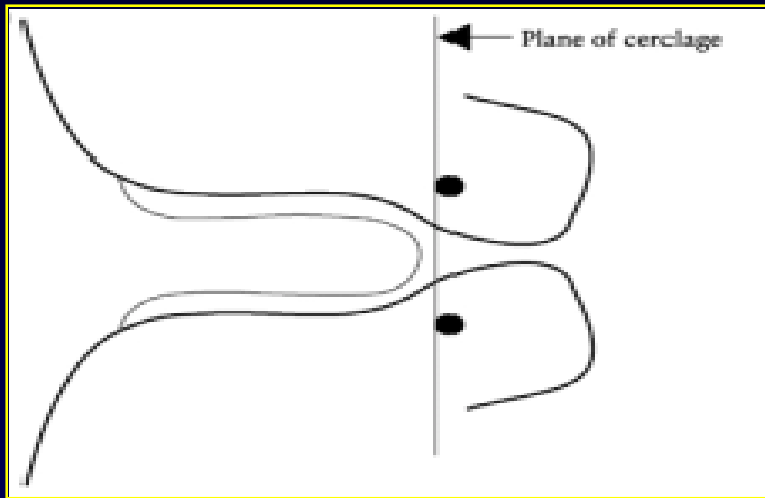
** > 30 mm: rate of PTB 4%

Triplet Gestation:

Length < 25 mm @ 14-20 w gestation had PPV 83% for PTB

*Maslovitz et al, J Ultrasound Med (2005); Vayssiere et al, Ultrasound Obstet Gynecol (2005)
Vayssiere et al, Am J Obstet Gynecol (2002); Guzman et al, Am J Obstet Gynecol (2000)
Yang et al, Ultrasound Obstet Gynecol (2000)*

Cervical Length Post Cerclage



- the residual cx length after cerclage placement:
 - <1.5 cm 70% SPTB < 32w
- “funneling to stitch” was present:
 - 65% SPTB <32w
 - regardless of indication for stitch placement

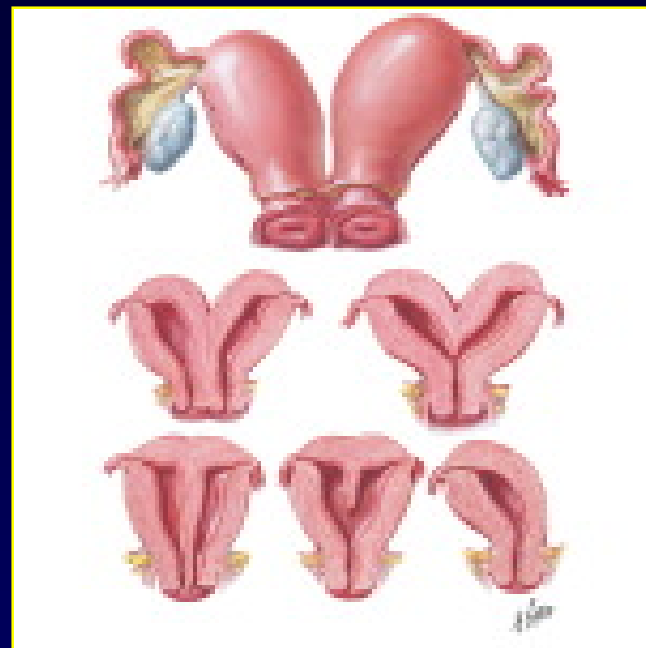
Seaward and Whittle (unpublished)

Fried et al, SMFM (2007)

O'Brien et al, Ultrasound Obstet Gynecol (2002)

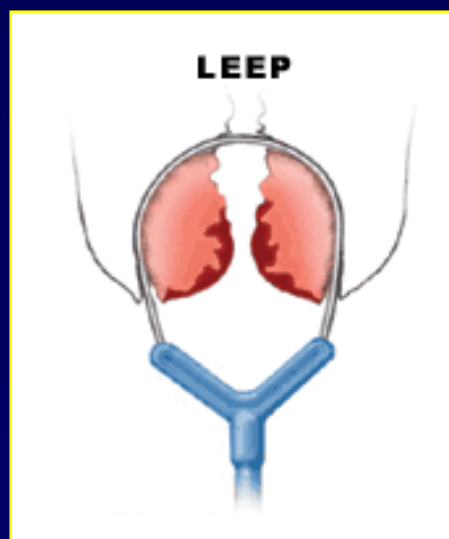
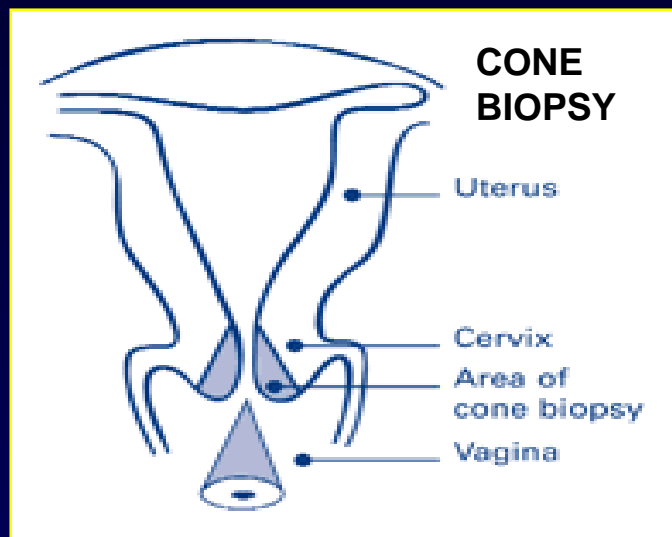
Cervical Length and Uterine Anomalies

- @ 14-23 w of gestation
cx < 25 mm: **risk of PTB was 50%**
- unicornuate uterus: shortest Cx and the highest rate PTB
- septate uterus: longest Cx and lowest rate of PTB
- PTB usually >30w GA



Overall; short cervical length has a 13-fold risk of PTB

Cervical Length and Cervical Surgery



1. Patients with previous Cx Sx have **shorter cx length** compared with controls
2. LEEP & Cone were associated with PTB - OR 3.45
3. Cx length **< 30 mm**
PPV 58.3%
NPV 97%

Cervical Length and PPRROM

- No relation b/w chorioamnionitis, neonatal sepsis
- After PPRROM: cx length <2.0 cm predicted latency <48h (68%)

? Can cx length predict PPRROM

Screening criterion	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Odds ratio	95% CI
Cervical length							
< 20 mm	18	67	43	43	67	1.5	0.5–4.1
< 15 mm	12	44	74	52	69	2.3	0.8–6.3
< 10 mm	9	33	90	69	68	4.8	1.3–17.5
< 5 mm	7	26	95	78	67	7.0	1.3–36.8
Cervical funneling							
> 25%	23	85	31	44	77	2.6	0.7–8.9
> 50%	13	48	67	48	67	1.9	0.6–5.0
> 75%	9	33	93	75	68	6.5	1.6–26.9
100%	6	22	95	75	66	5.7	1.1–30.8
Cervical length and funneling							
< 10 mm + > 75%	9	33	90	69	68	4.8	1.3–17.5

Cervical Length and Fetal Therapies

- Cx length < 30 mm at time of MPR (3 to 2) predicts PTB
 - PPV 67% for delivery < 33w

- TTTS treated by laser, cx length before treatment <30 mm significantly associated with PTB independent of:
 - parity
 - intrauterine death of one fetus
 - disease severity
 - volume of amnioreduction

Fait et al, J Clin Ultrasound (2005)

Robyr et al Ultrasound Obstet Gynecol (2005)

Rebarber et al, Am J Obstet Gynecol (2001)

Cervical Length and Polyhydramnios

Goal: To determine if cx length is related to severity of poly & GA @ delivery

Method: prospective cohort
n=92
AFI >20

Results: Mean cx length 3.7 cm
Gradual shortening with GA

No association with severity of AFV

Cut off <1.5 cm – lower GA @delivery (n=5)

Clinical Utility of Identified Short Cervix

Asymptomatic Women
Low / High Risk

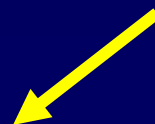
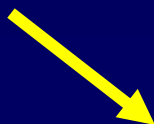


Increased monitoring
Rationale use of cerclage
Rescue cerclage
Progesterone Rx
Education

Symptomatic Women



Antenatal steroids
Tocolysis
In utero transfer to 3^o care
Education

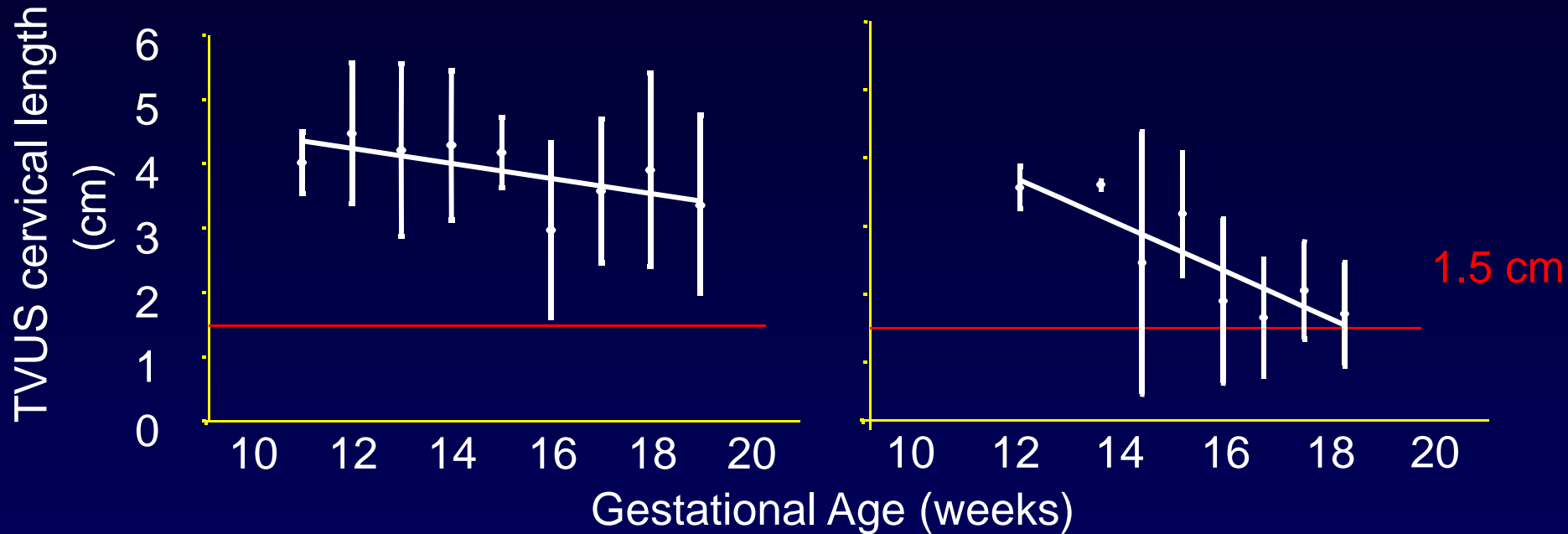


Improved Neonatal Outcome

A. The Use of Cerclage

- 1) Cx < 1.5 cm & at low risk for PTB (by history):
no benefit
- 2) Cx < 1.5 cm & at high risk for PTB (by history):
effect controversial
- 3) Cx < 1.5 cm and membranes exposed/prolapsed
“rescue” cerclage beneficial
- 4) High risk patients with serial TVUS of the cervix length followed by cerclage in those who shortened the cervix:
reasonable alternative
(uncontrolled studies, our clinic data)

Indicated cervical cerclage (n=75)



No intervention



Mean GA 36.8 \pm 2.7 weeks

Mac Donald cerclage



Mean GA 35.3 \pm 4.9 weeks

No difference in baseline cx length, RF, neonatal outcome

B. Antibiotics

- asymptomatic women, $cx < 2.5\text{cm}$: *no benefit*

C. Prophylactic Tocolysis:

- indomethacin
 - progesterone
-

Short cervix on ultrasound: does indomethacin prevent preterm birth

Berghella et al, AJOG; 2006

- rationale: short cervix = uterine activity
- individual data from control group of cerclage RCT

PTB rate: 29.3% indo vrs 42.5% no indo
decreased rate $< 24\text{w}$

Progesterone and the risk of preterm birth among women with a short cervix

Fonseca et al, NEJM; 2007.

Goal: To determine progesterone decreases the risk of PTB in women with short cx midgestation

Method: 250 unselected women
20-25w TVUS Cx <1.5 cm
double blind: placebo v progesterone

Results: Significant reduction in SPTB <34w
19.2% v 34.4%

Issues: neonatal outcome
subpopulations: parity, gestation number, OBHx

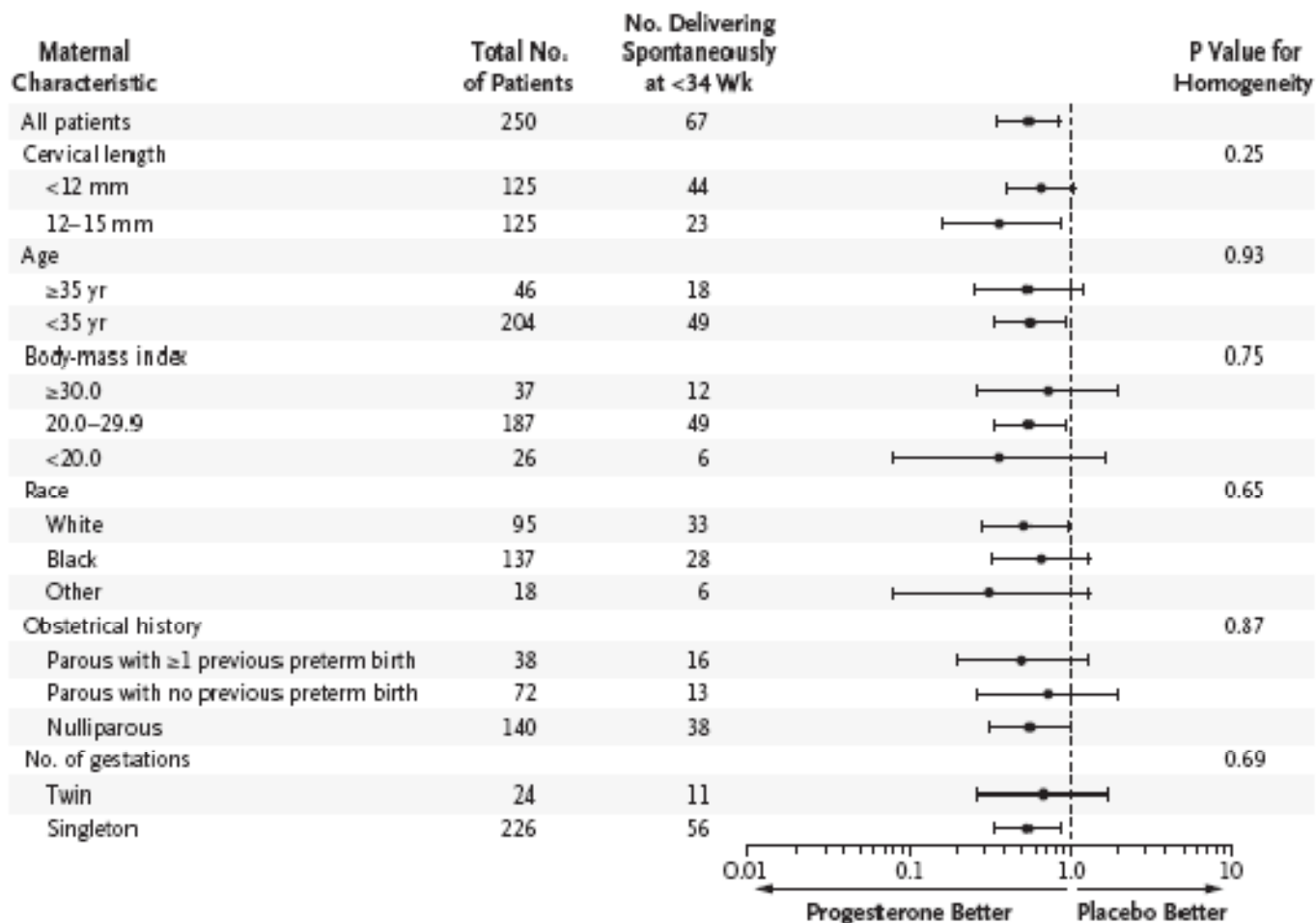


Figure 3. Relative Risk of Spontaneous Birth before 34 Weeks Associated with Progesterone Use in Relation to Maternal Characteristics at the Time of Randomization.

Filled circles indicate the relative risks, and bars the 95% confidence intervals. The Mantel–Haenszel test was used to test for homogeneity. The body-mass index is the weight in kilograms divided by the square of the height in meters.

Prevention
SPTB
Clinic
Protocol

At Risk Patient

Speculum: texture, dilatation
Swab: cervicovaginal x 2
q 4w urine c/s
Placentation testing

Screening TVUS
@ 14-16w

TVUS q 1-2 w intervals
until 28w

<2.5 cm
? Cerclage

>2.5 cm
Repeat TVUS

Repeat Speculum @24w
Consider steroids

Shortening cx
Cerclage
+/- tocolysis

Stable cx
Ext Mx

Prevention
SPTB
Clinic
Protocol

Low Risk Patient: Cervix < 2.5 cm

Speculum: texture, dilatation

Swab: cervicovaginal x 2

q 4w urine c/s

Placentation testing

Repeat TVUS x 1w

TVUS q 1-2 w intervals
until 28w

Shortening cx

Cerclage

? Progesterone

Stable cx

Ext Mx



Current Status and Clinical Utility of Cervical Assessment

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Fetal Medicine Unit

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