PRETERM LABOR – CURRENT APPROACHES TO DIAGNOSIS AND MANAGEMENT

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PRETERM BIRTH IN THE U.S.

- U.S. preterm birth rate = 9-12 %
- U.S. ranks 20th in perinatal mortality among the industrialized nations
- incidence increasing
- mortality decreasing
- morbidity increasing….

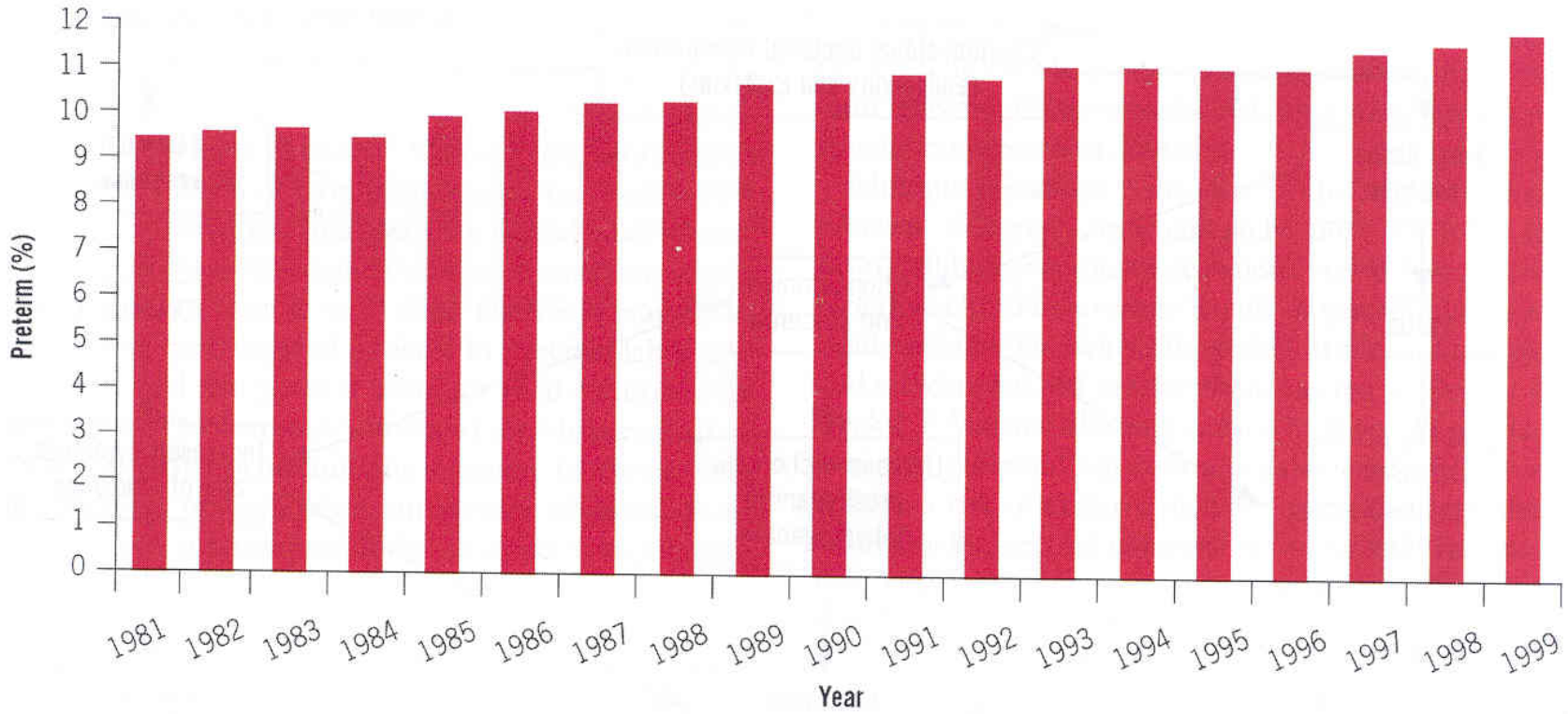
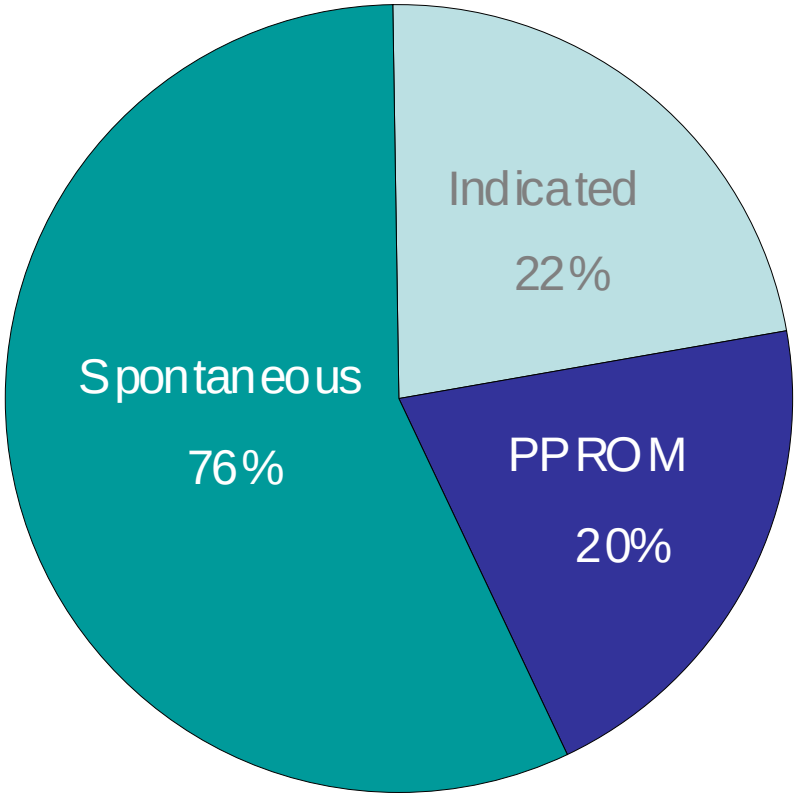


Figure 1. Incidence of preterm birth in the United States, 1981–1999. Source of data: National Center for Health Statistics.[97]

Goldenberg. Management of Preterm Labor. Obstet Gynecol 2002.

Categories of Preterm Births



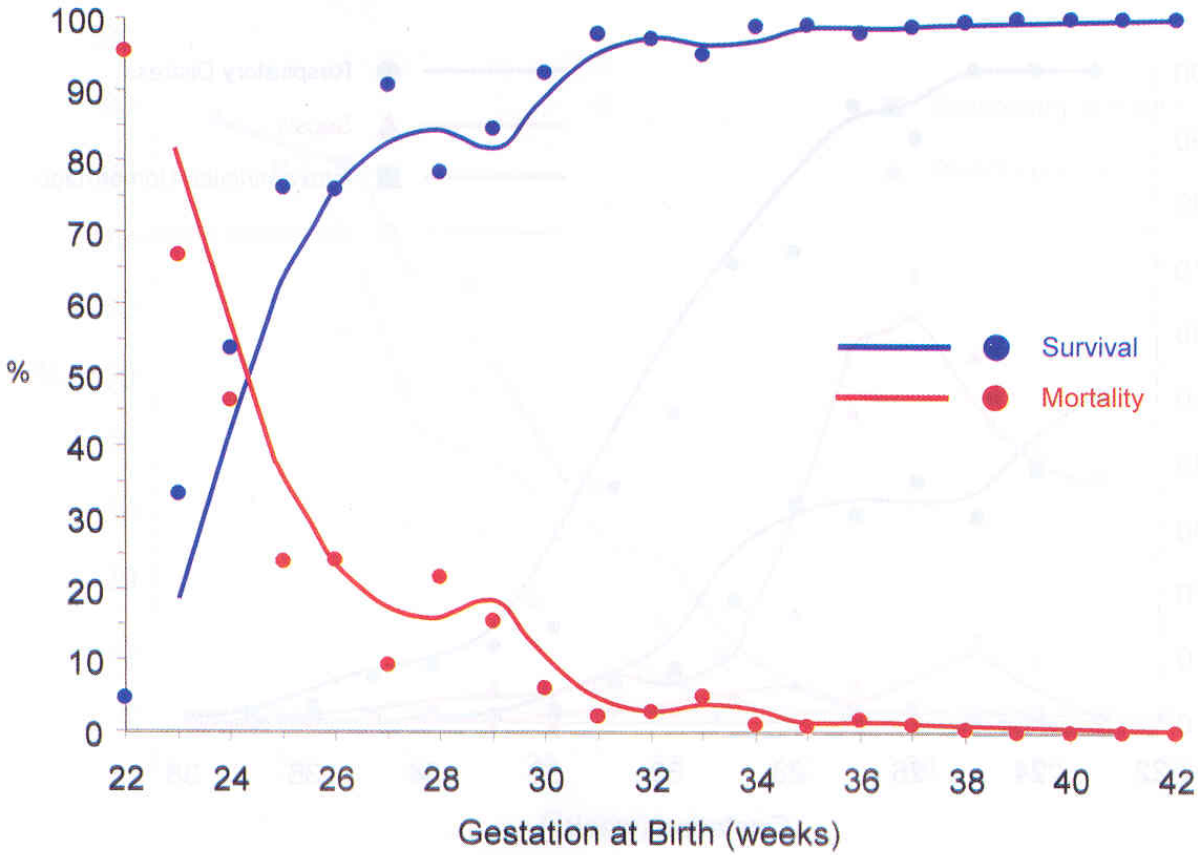


Figure 1. Survival by gestational age among live-born resuscitated infants. Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee. Curves smoothed by 2-point average.

Mercer. Treatment of Preterm PROM. Obstet Gynecol 2003.

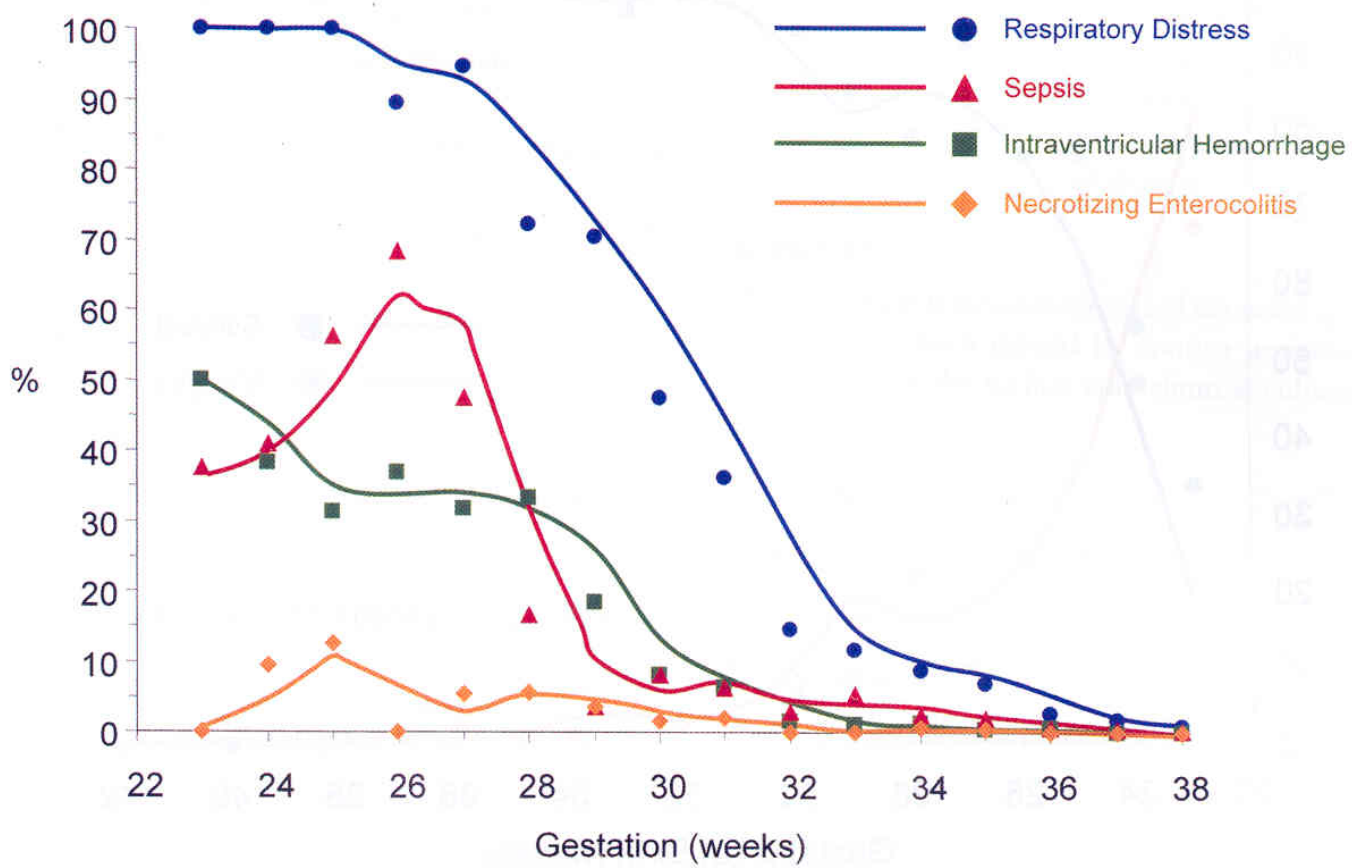


Figure 2. Acute morbidity by gestational age among surviving infants. Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee. Curves smoothed by 2-point average.

Mercer. Treatment of Preterm PROM. Obstet Gynecol 2003.

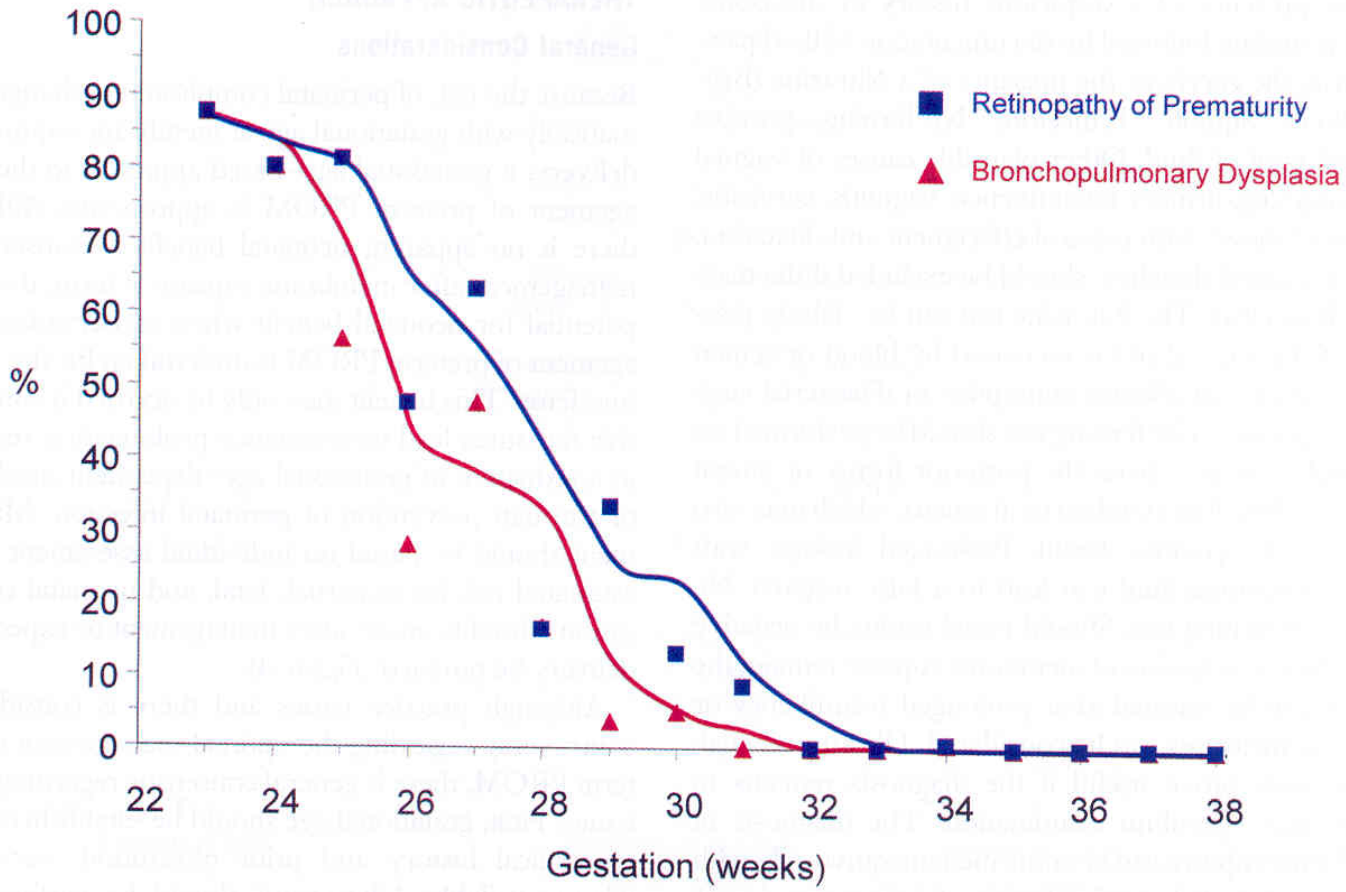


Figure 3. Chronic morbidity by gestational age among surviving infants. Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee. Curves smoothed by 2-point average.

Mercer. Treatment of Preterm PROM. Obstet Gynecol 2003.

DEFINITION OF PRETERM LABOR
(Creasy and Gonik: AJOG 154:3, 1986)

1. GA 20-37 weeks plus
2. UC 4 in 20 min. or 8 in 60 min. plus

3 a. SROM or

b. cx 2 cm dilate or

c. cx 80% effaced or

d. definite cx change

(requires 1 + 2 + a or b or c or d)

PTL: MANAGEMENT BEDREST

- No prospective RCT showing benefit
- 4 twins studies:
  - -(2) no benefit
  - -(2) increase in PTB
- Downside:
  - -muscle weakness, osteoporosis, DVT
  - -guilt, unemployment, marital, etc.

PTL: MANAGEMENT HYDRATION/SEDATION

- Theory: Henry-Gauer reflex (ADH)
- 2 RCT for hydration (1L LR): no benefit
- 1 RCT for sedation (morphine): no benefit
- Downside: overhydration + tocolytics
  ---> pulmonary edema

TOCOLYTICS FOR PTL META-ANALYSIS -(OG-1999)

- N=18 studies (N=1406 patients)
- decreased risk of del 48 h: OR=.47 (.29-.77)
- “ “ “ 7 d: OR=.60 (.38-.95)
- did not reduce rate of PNM: OR=1.22
- “ “ “ RDS: OR=.82
- “ “ “ BWt<2500g: OR=.62

TOCOLYTICS FOR PTL BETA-MIMETICS

- Cochrane (2004) – 11 trials (n=1332)
- PNM OR=1.00 (.72-1.06)
- RDS OR=0.87 (.71-1.08)
- Del <48 h OR=0.63 (.53-.75)*
- Del <7 days OR=0.67 (.48-1.01)

BETA-MIMETICS SIDE EFFECTS

MATERNAL

-tachycardia, diastolic hypotension, hypokalemia, hyperglycemia, tremor, SOB, chest pain, pulmonary edema

FETAL

-fetal tachycardia, hypoglycemia

Beta-Mimetics Clinical Use

- Terbutaline probably best used for triage:
  - terbutaline 0.25 mg subcut x1-2
- If the contractions stop with that, it's probably not true preterm labor
- Longer use probably not justified because of side effect profile and availabililty of other agents

TOCOLYTICS FOR PTL MgSO4

- Cochrane (2002) – 3 trials (n=190)
- PNM OR=1.83 (0.7-4.8)
- RDS OR=1.09 (0.98-1.22)
- BWt>2500 OR=1.06 (0.6-1.9)
- Del <48 h OR=0.57 (0.3-1.63)

MgSO4 – Side Effects

- MATERNAL
  - flushing, hypotension, vomiting, muscle weakness, desaturation, diplopia, headache

  FETAL

  -bradycardia, loss of variability, “floppy baby”

  -neuroprotective vs. harmful effect?

  RECOMMENDATION:

  DON’T use, “it’s s-o-o ’90’s!”

TOCOLYTICS FOR PTL NIFEDIPINE

Cochrane (2003) 12 trials (n=1029)

- 48-h delay in delivery 0.72 (.53-.97)*
- 7 day delay in delivery 0.76 (.60-.97)*
- Reduction in IRDS 0.63 (.46-.88)*
- superior compared to betamimetics

Nifedipine – Side Effects

- MATERNAL
  - flushing, headache, dizziness, hypotension, pulmonary edema
- FETAL
  - decels secondary to maternal hypotension

Nifedipine Clinical Use

- Nifedipine 30 mg po loading dose, followed by 20 mg po in 90 minutes – OR-
- Nifedipine 10 mg po q 20 min x4
- Followed by maintenance:
- Nifedipine 10 mg po q6 h x 48 hours
- Reduce dose or stop if hypotension or intolerable headache

TOCOLYTICS FOR PTL INDOMETHACIN

- Cochrane (2005) – 13 trials (n=713)
- PNM OR=1.48 (0.2-9.2)
- RDS OR=0.61 (0.2-2.3)
- Del <48h OR=0.27 (.08-.96)*
- Del <7 days OR=.88 (.52-.1.46)

Indomethacin – Side Effects

- MATERNAL
  - gastritis, reflux, nausea/vomiting
- FETAL
  - constriction of the ductus arteriosus and oligohydramnios may be seen w/ >48 h use, but long term effects (IVH, NEC, renal failure) no different than controls if <48 h use

TOCOLYTICS FOR PTL USE OF INDOMETHACIN

- GA≤32 weeks if >1 dose to be given
- no oligohydramnios
- loading dose: 100 mg rectal suppository or
- 50 mg orally
- maintenance: 50 mg po q6h
- max dose: 400 mg in 48 hrs
- symptomatic tx if GI side effects

Cost-Effectiveness of Tocolytics

- Hayes. AJOG 2007: 19 trials (n=1073)

Drug	Side Effx	Cost
Indomethacin	11%	$ 15
Nifedipine	27%	$ 17*
MgSO4	22%	$198
Terbutaline	58%	$399

RISK OF IRDS

28 weeks 65%

30 weeks 50%

32 weeks 40%

34 weeks 22%

35 weeks 7%

36 weeks <1%

EFFECTS OF CORTICOSTEROIDS

OXFORD DATABASE OF PERINATAL TRIALS (N=23)

- Reduction overall of IRDS (N=1635)

  OR = 0.49 (.41-.60)

- Reduction < 31 weeks

  OR = 0.38 (.24-.60)

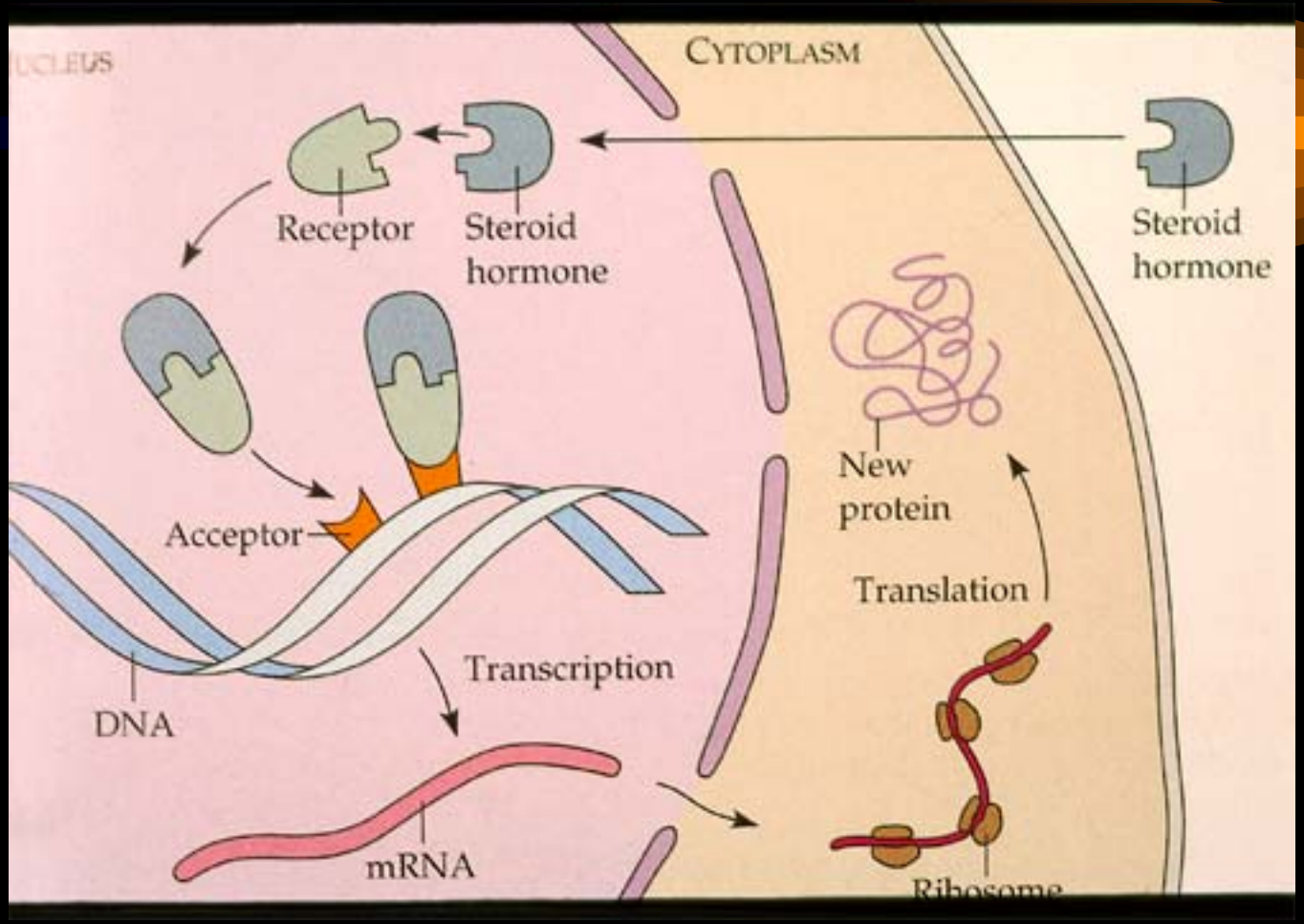
EFFECTS OF CORTICOSTEROIDS

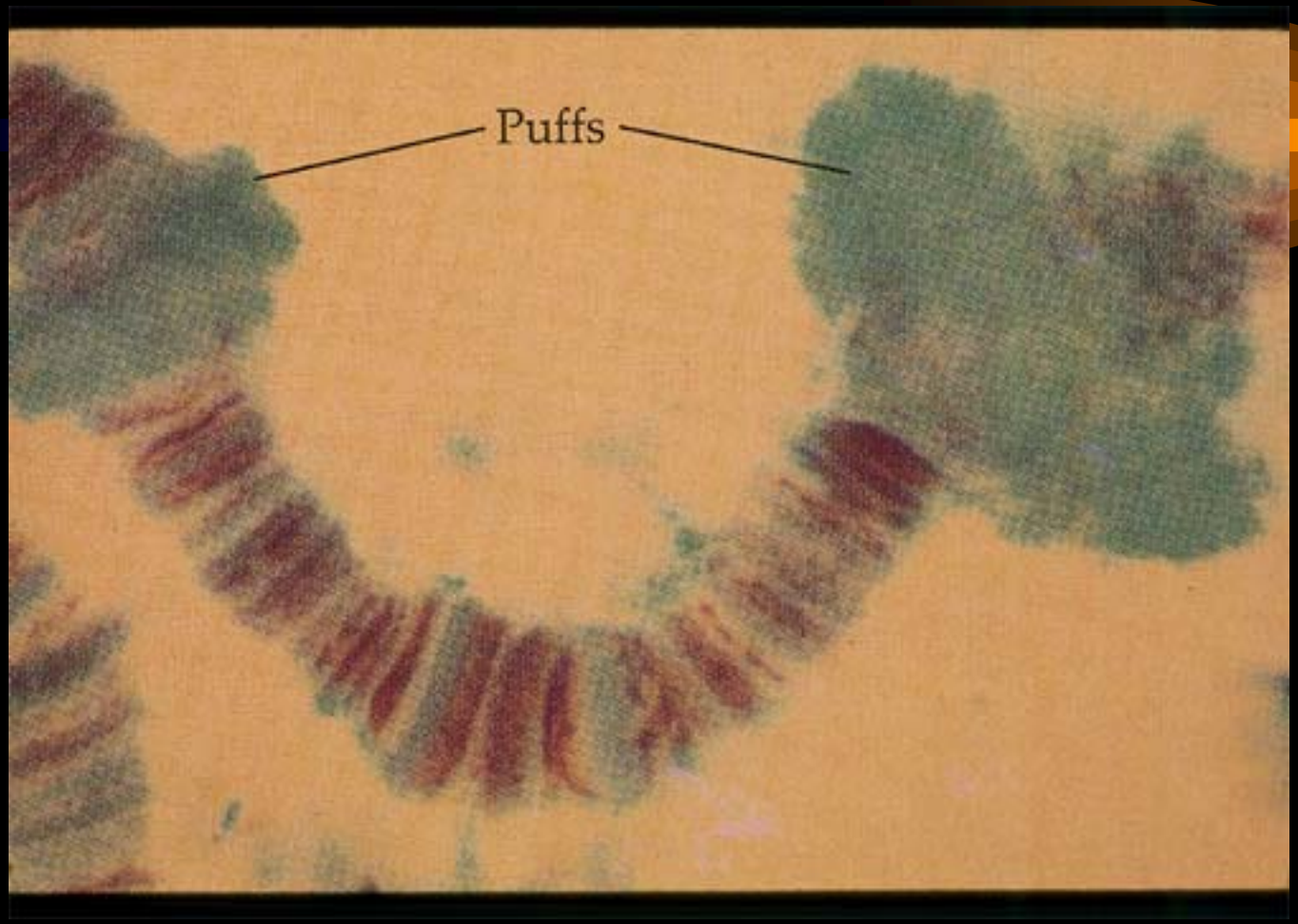
OXFORD DATABASE - IRDS - TIME

- Reduction IRDS (24h $\rightarrow$7d)

  OR = 0.31 (.23-.42)
- Reduction IRDS (> 7d)

  OR = 0.69 (.50-.94)


CYTOPLASM
Receptor
Steroid hormone
Steroid hormone
New protein
Acceptor
Translation
Transcription
DNA
mRNA


Puffs

EFFECTS OF CORTICOSTEROIDS

OXFORD DATABASE - OTHER OUTCOMES

- neonatal death OR= .59 (.47-.75)
- IVH = .45 (.21-.97)
- neurologic abn = .61 (.34-1.08)
- NEC = .37 (.17-.69)

EFFECT OF CORTICOSTEROIDS in PPROM -OXFORD DATABASE

- IRDS after PPROM = .55 (.40-.75)
- MAT. INFX after PPROM = 2.10(.69-8.47)
- NN. INF after PPROM = 1.61(.87-2.98)

CORTICOSTEROIDS and INFECTION - Oxford Data Base

- maternal infection = 1.11 (.81-1.51)
- neonatal infection = .83 (.54-1.26)

How babies are REALLY delivered

Normal Pattern of Uterine Activity Night: Day Ratio

- 20 wks 1.8:1
- 30 wks 2.3:1
- 40 wks 2.8:1
- 67% of all contractions occurred after dark

Normal Pattern of Uterine Activity

- Only 26% had contractions
- 85% of those had only 1-3 contractions/hour
- Day animals deliver at night
- How helpful is bedrest?

Normal Pattern of Uterine Activity Effect of Activity, Sex, Stress

- No increase with exertion ($^{-}$.1%)
- Rest decreased UC X 3 hours ($^{-}$1.1%)
- Sex increased UC X 1 hours ($^{+}$5.5%)
- Stress had no effect ($^{+}$0.2%)

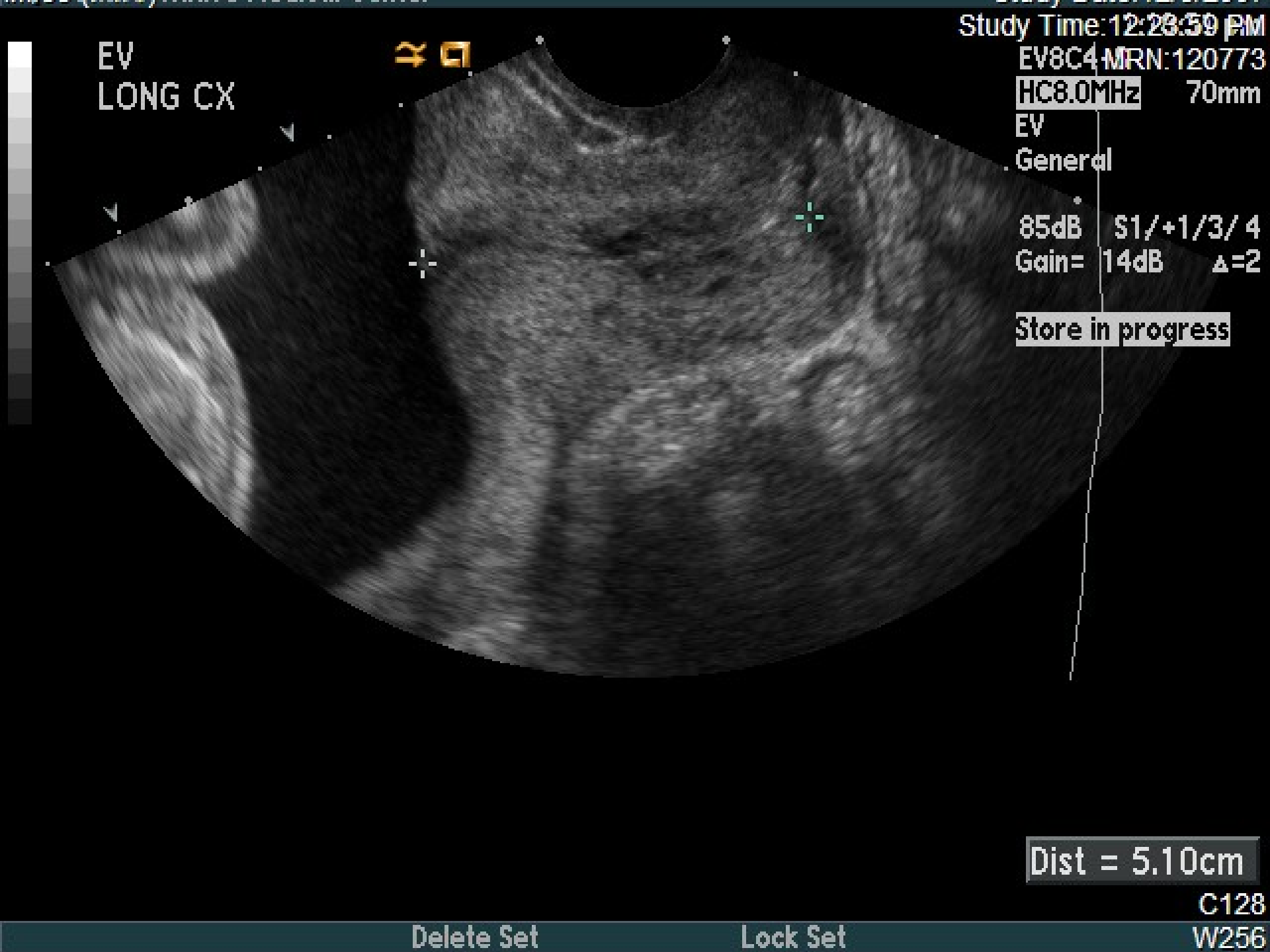
Steve Anderson 2005

Case #1

- 25 y/o G2P1 at 29 weeks presents with uterine contractions every 3 min x last 3 hrs. On exam her cx is FT dilated, 50% effaced, vertex -3 station. The monitor shows q3' UC that are perceived, but not painful. Is she at risk of PTB?

So…, is this woman really having PTL? Two Useful Tools

- Transvaginal Cervical Length
- Fetal Fibronectin


EV
LONG CX
Study Time:12:28:59 PM
EV8C4 MRN:120773
HC8.0MHz 70mm
EV
General
85dB S1/+1/3/ 4
Gain= 14dB Δ=2
Store in progress
Dist = 5.10cm
C128
Delete Set
Lock Set
W256

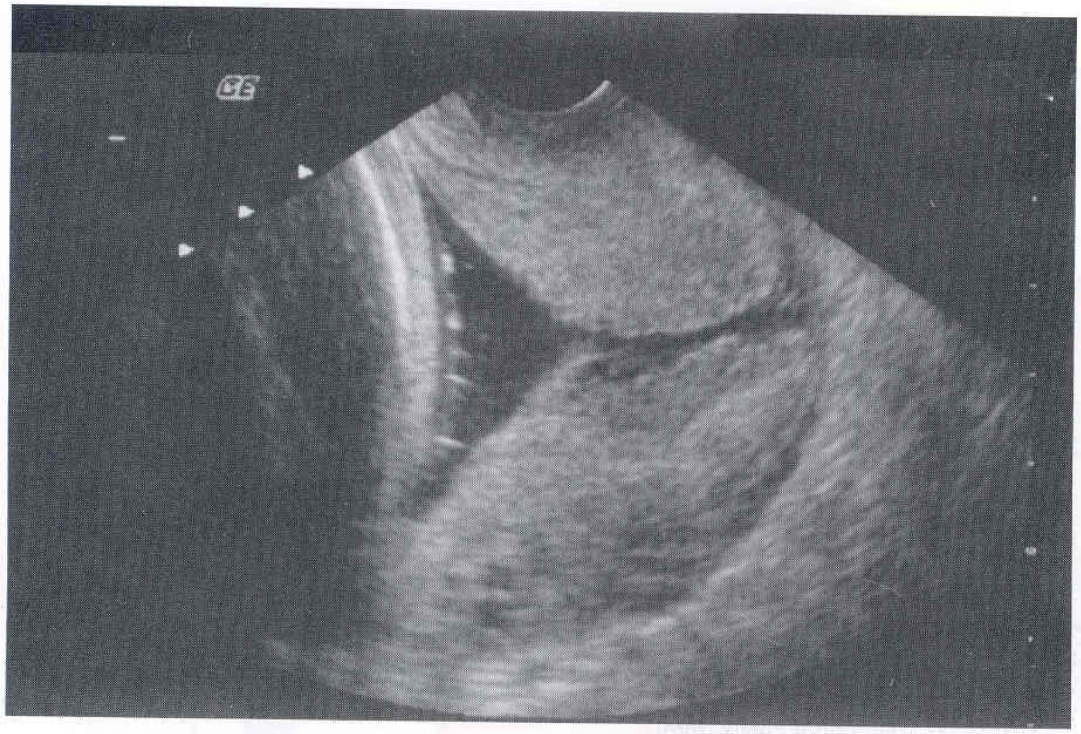


Figure 3. Transvaginal ultrasound image of the cervix obtained from a woman with symptoms of preterm labor. The image supports a diagnosis of preterm labor because of the length (23 mm) and the Y-shaped appearance of the cervix.

Iams. Early Detection of Prematurity. Obstet Gynecol 2003.


EV
LONG ML
I
10:53:40 AM
EV8C4-S111407-536
HC8.0MHz
80mm
EV
General
85dB
S1/+1/3/ 4
Gain= 3dB
Δ=2
Store in progress
Dist = 2.22cm
C128
W256
Not for diagnostic use
Home Set
Home ACUSON

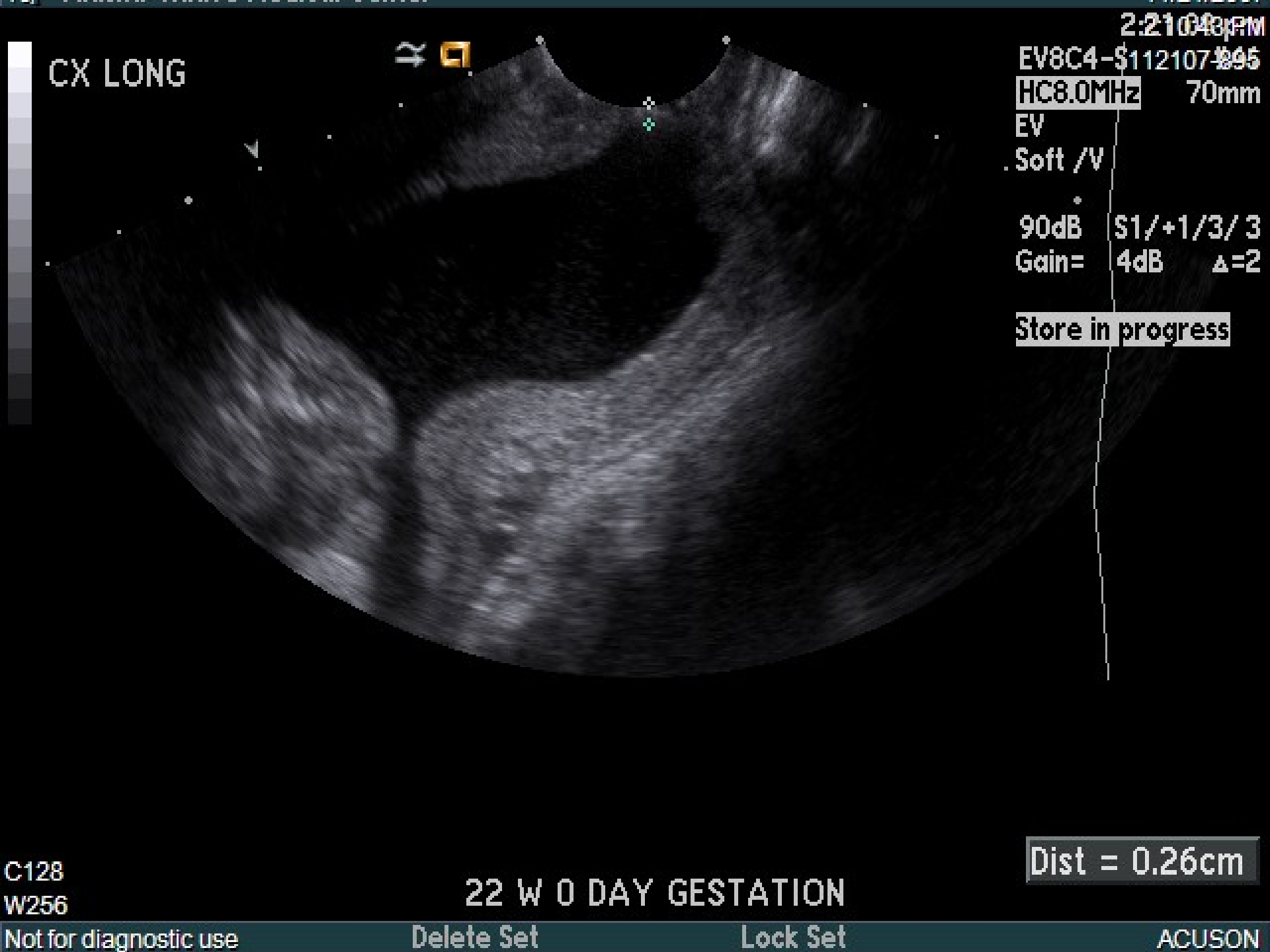
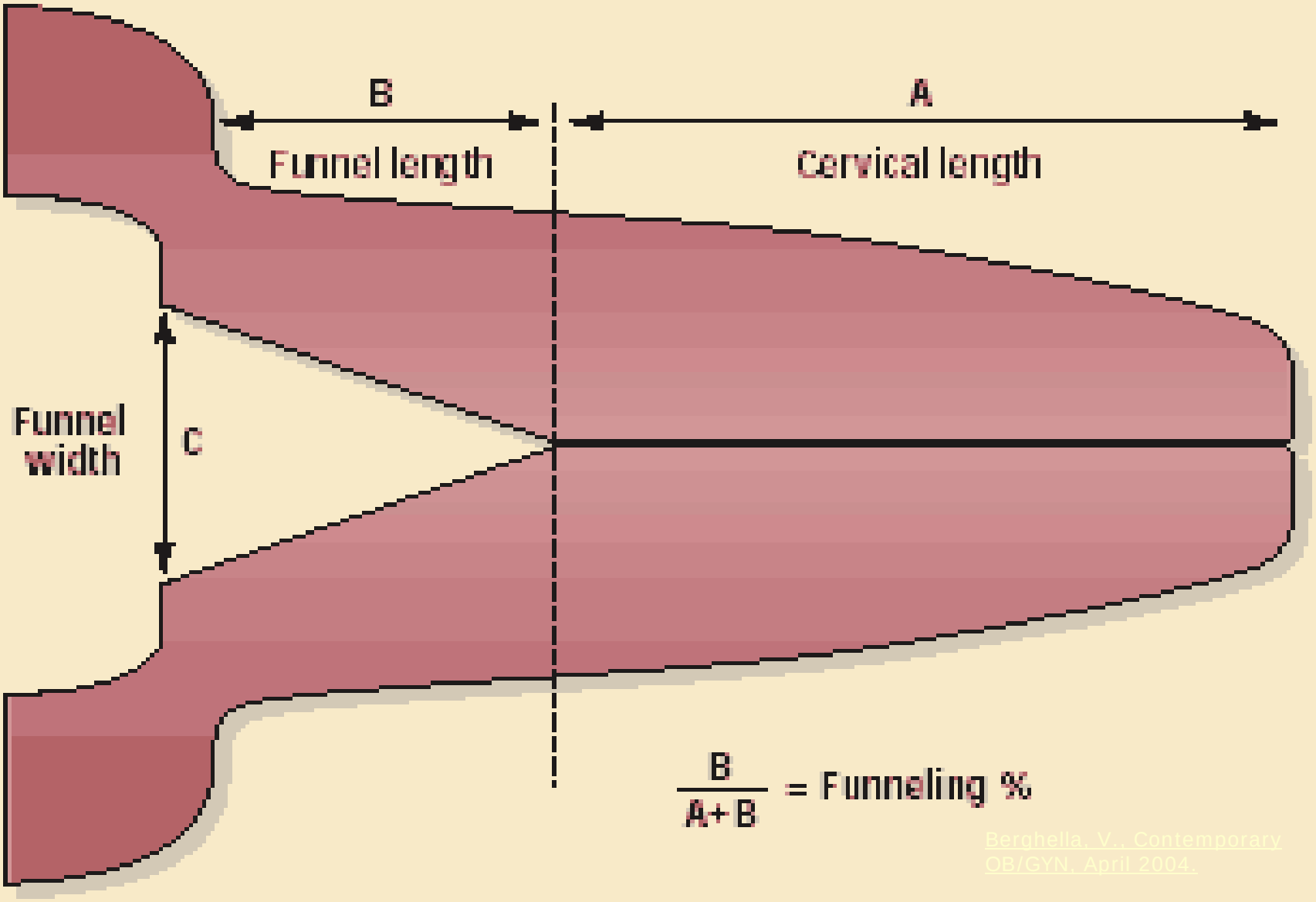

CX LONG
2:21:43PM
EV8C4-$112107-295
HC8.0MHz
70mm
EV
Soft /V
90dB
S1/+1/3/ 3
Gain=
4dB
Δ=2
Store in progress
Dist = 0.26cm
C128
W256
22 W 0 DAY GESTATION
Not for diagnostic use
Delete Set
Lock Set
ACUSON

FIGURE 2. How to calculate funneling on transvaginal ultrasound



Berghella, V., Contemporary OB/GYN, April 2004.

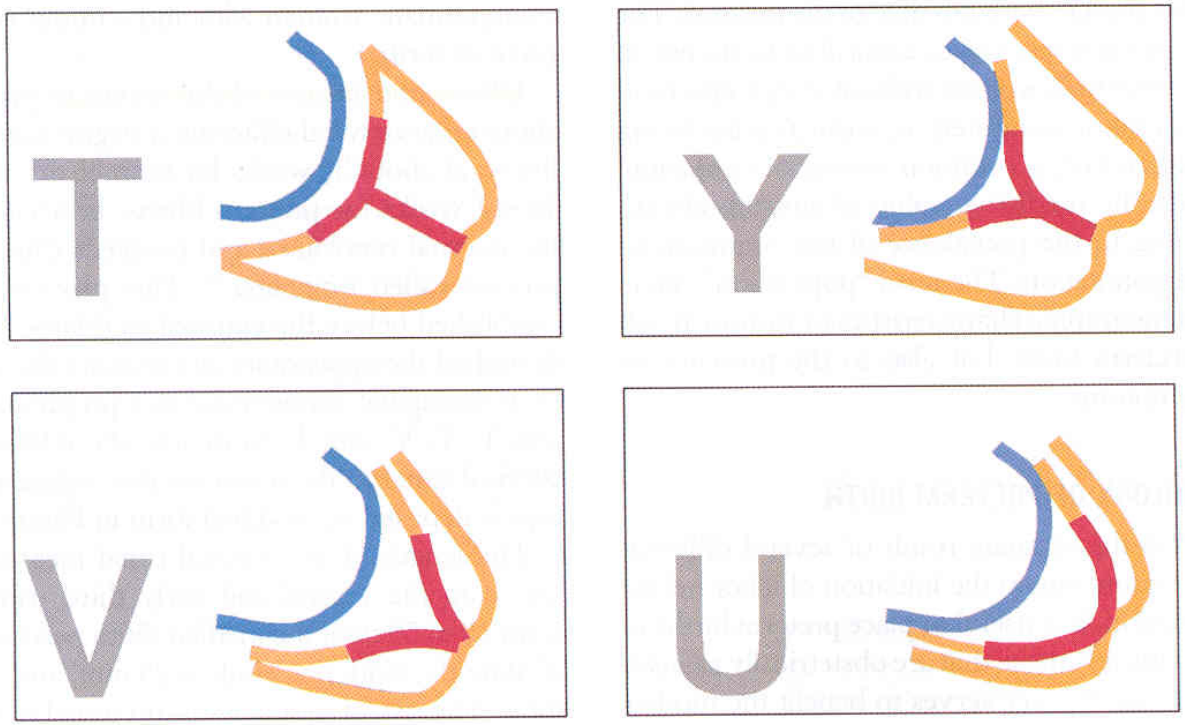


Figure 1. Schematic to display the process of cervical effacement as it proceeds from the internal os, caudad toward the external os, as seen on transvaginal sonography. The letters T, Y, V, and U depict the relationship between the lower uterine segment and the cervical canal. Gray, cervical configuration; blue, fetal head; orange, cervix; red, cervical change. (Modified with permission from Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: A new perspective. J Ultrasound Med 1995;14:719–24. Copyright © 1995 American Institute of Ultrasound in Medicine.)

Iams. Early Detection of Prematurity. Obstet Gynecol 2003.

How to measure the cx length with transvaginal sonography

- Empty bladder
- Probe in the anterior fornix
- Avoid excess pressure on cx
- Endocx canal visualized
- Enlarge image (cx 2/3 of screen)
- Average 3 measurements
- Appy abdominal compression and re-measure

Cervical Length (24 - 28 WKS) Risk of Preterm Delivery

- NL : 3.5 ± 8 cm
- < 10th % : < 2.5 cm
- Risk of PTD: RR - 6.2
- funnel (> 1.5 cm) : RR - 5.0

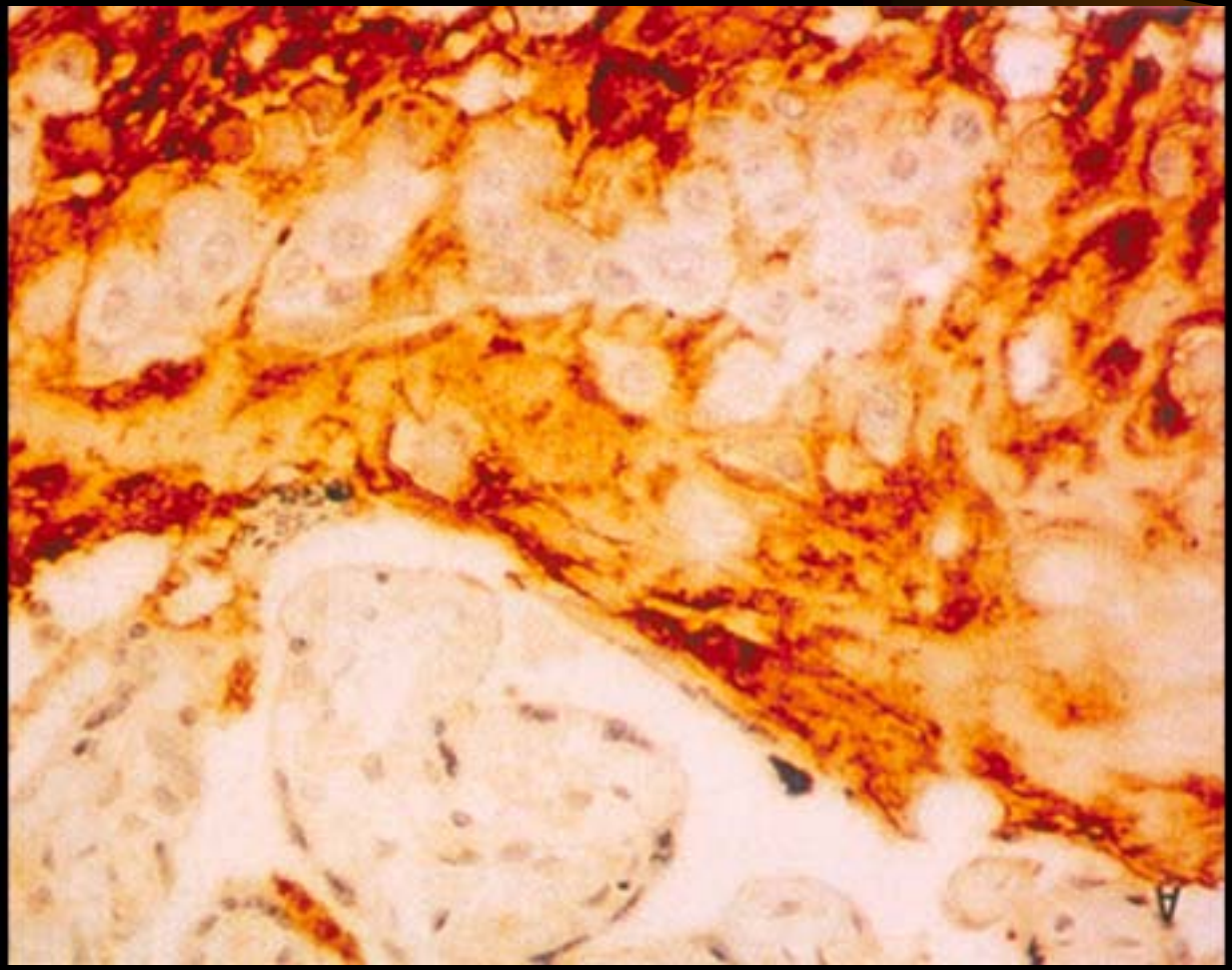
Cervical Length and the Risk of PTB in Asymptomatic Women

CX LENGTH	PROB. PTB
>3 cm	7%
2 cm*	15%
<1 cm	42%

- *PPV only 18%, but NPV 96%

FETAL FIBRONECTIN WHAT IS IT?

- extracellular matrix protein
- concentrated at the chorio-decidual juncture
- extracellular interface between mom & fetus
- proteolysis during labor ➲ “leaks” thru cervix



fFN in ASYMPTOMATIC WOMEN - MFMU NETWORK - 1994

- Cx specimen 24 wks (N=2208) (4% pos.)

GA	<30 wks	<32 wks	<35 wks
PTB	0.9%	1.7%	4.7%
OR	42	23	11
SENS	52%	37%	20%

fFN in SYMPTOMATIC WOMEN
PEACEMAN - AJOG (1997)

- symptomatic patients (n=763) - 24-34 weeks

outcomes: delivery	<7 days	<37 weeks
NPV	99.5%	85%
PPV	13%	43%

FETAL FIBRONECTIN
CLINICAL USE

- Intact membranes
- NO bleeding
- NO coitus/24 hours
- NO lubricant
- Collect from posterior fornix
- Leave swab x 10 seconds

Cervical Length + fFN in the triage of women with preterm contractions

- CL<1.5 cm -→ 51% PTB in next 7 days
- CL>1.5 cm -→ 1% PTB
- CL<1.5 cm + (+)fFN -→72% PTB
- CL>1.5 cm + (-)fFN -→ 0.6% PTB
- "If the cervix is long and the fFN is negative, you can say 'So long'"!

CHORIOAMNIONITIS PATHOGENESIS

- ROM ➲ ascending infection

- OR -

- Ascending infection ➲ ROM
- role of microbial colonization and production of collagenase and elastase resulting in ROM

ANTIBIOTICS FOR PTL-EFFICACY RCT (N=860)

- Erythro, Amp, clinda
- Delay in del. ? - NO - 4,
- YES - 4
- Increase BWT? - NO - 8/8

ANTIBIOTICS AND PPROM KIRSCHBAUM - (n=2481)

- increased PROM - del. interval
- ?decreased NN sepsis
- No reduction NN mortality

ANTIBIOTICS FOR PPROM MATERNAL OUTCOMES (n=649)

	OR	CI
• Latency > 1 week	1.97	(1.48 - 2.61)
• Chorioamnionitis	0.45	(.33 - .60)
• PP infection	0.63	(.41 - .97)

ANTIBIOTICS FOR PPROM INFANT OUTCOMES (n=649)

	OR	CI
• Perinatal death	0.74	(.50 - 1.11)
• IRDS	0.90	(.71 - 1.15)
• Sepsis	0.57	(.36 - .88)

ANTIBIOTICS AND PPROM

- ORACLE I (2001) n=4826
- erythromycin 250 mg qid x 10 d
- co-amoxiclav 250/125 mg “ “ -vs- placebo
- primary outcome composite:
  - neonatal death
  - chronic lung disease
  - major CNS abnormality

ORACLE I: ANTIBIOTICS/PPROM
Placebo vs. Erythro vs. Amox

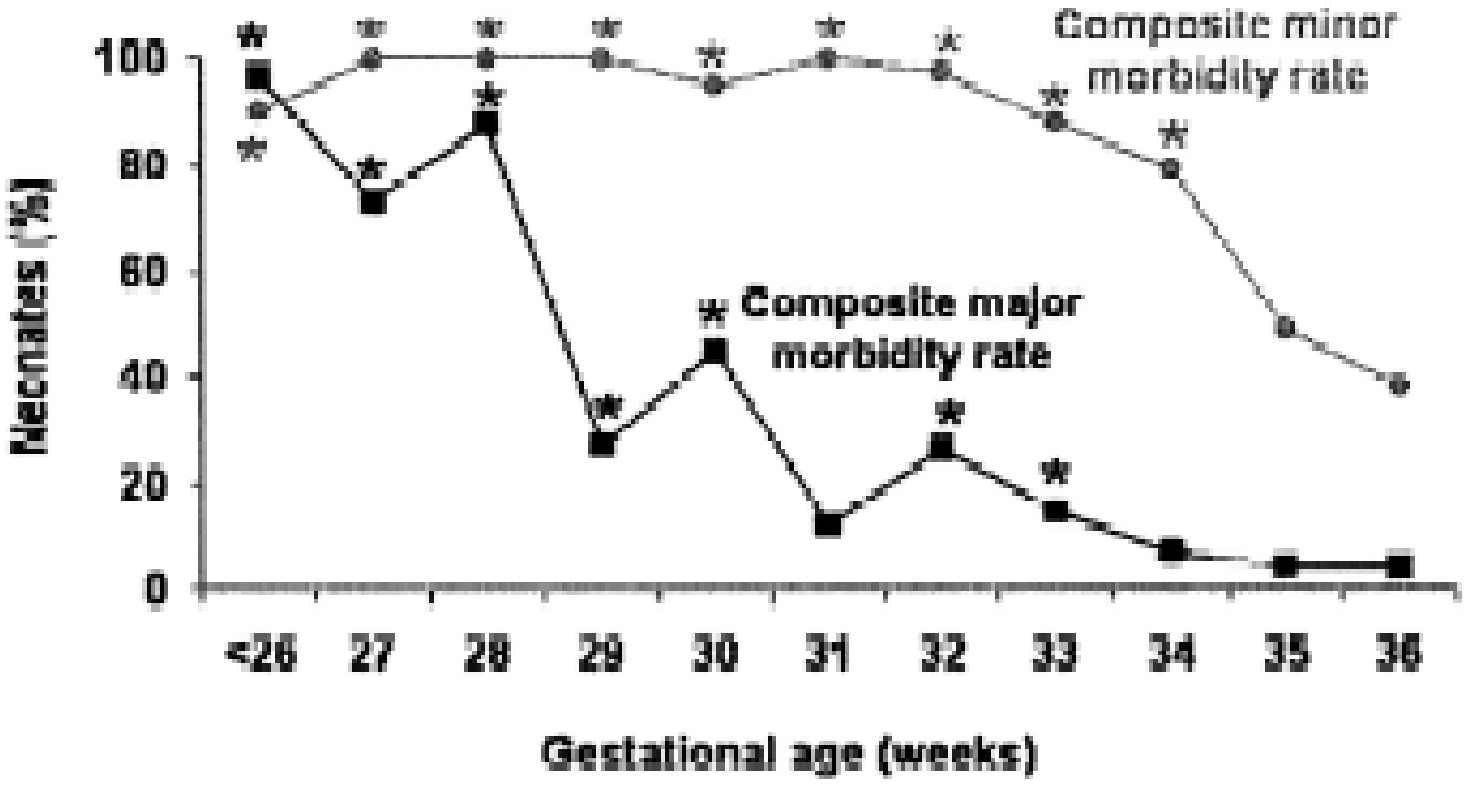
• Del<48 hrs	41%	35%	31%*
• IRDS	22	20	20
• Sepsis	8	6	7
• NEC	0.5	0.7	1.9*

ANTIBIOTICS AND PTL with Intact Membranes

- ORACLE II (2001) N=6295
- same composite primary outcome
- erythromycin, co-amoxiclav, placebo
- 5.6% vs. 5.0% vs. 5.0%
- antibiotics of no value for PTL-IM

IS THERE AN OPTIMAL TIME TO DELIVER WOMEN WITH PPROM?

- When are the infant's risks of IRDS outweighed by the risk of sepsis?
- What about minor morbidity and LOS?
- 6 studies (n=1,087) PPROM 32-36 wks
- less chorio/sepsis if induced immediately
- no significant benefit to expectant management after 34 weeks



Lieman. Preterm PROM and Neonatal Morbidity. Obstet Gynecol 2005.

BACTERIAL VAGINOSIS AS A RISK FOR PRETERM BIRTH

- Leitich (2003) – meta-analysis#1
- -18 studies (n=20,232)
- BV increased the risk of PTB:
  - OR = 2.19 (CI: 1.54-3.12)
  - (BV was not associated with PNM however)

ANTIBIOTIC TREATMENT OF BV AND PRETERM BIRTH

- Leitich (2003) –meta-analysis#2
- 10 studies (n=3,969)
- Antibx tx of BV did not reduce PTB:
  - OR=.83 (CI: 0.22-1.12)
  - (in a subset of 338 high-risk women, tx for >7d did reduce PTB: OR=.42 (CI: .27-.67)

RCT of Metro and Erythro to Prevent Preterm Birth in fFN(+) Women MFMU/NICHD -2003

- n=16,317 women: 715 (4.3%) were fFN(+)
  100 (14%) were BV(+)
- screened at 21-26 wks
- tx w/ metro 250 tid + erythro 250 qid x 10d
- no difference in PTB rate, even if BV(+):
  - OR=1.17 (CI: .80-1.70)
  - subset w/ BV: OR=.84 (.41-1.74)

PERIODONTAL DISEASE AND PRETERM BIRTH: "The Perio-Premie Connection"

- theory: gingivitis-→LPS-→PGE-→labor
- 10 studies (n=2,559)
- association between perio and PTB:
- OR ranged from 2.7 to 7.9
- only 3 intervention trials-→more needed
- it's good to go to the dentist if you're pg…

PREVENTING PTB: the future? 17a-OH-Progesterone

- RCT (n=463 high risk women)
- prior sPTB, enrolled <20 wks
- weekly 17P 250 mg vs. placebo to 36 wks
- PTB<37 wks: 36 vs. 55% (RR=0.66)*
- PTB<32 wks: 11 vs. 20% (RR=0.58)*
- decreased NEC, IVH, O2 need

- *p<.01 (Meis-NEJM 2003)