

# Prevention of Preterm Delivery

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## Learning objectives

- Significance and statistics
- Prediction of PTD
- Etiology
- Prevention
  - Antibiotics
  - Cerclage
  - progesterone
- Tocolytic Treatment

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## Preterm delivery and Perinatal Mortality

- Incidence 12% and rising (IVF)
- 75% of perinatal morbidity and mortality for infants born without congenital anomalies
- 1:5 children with mental retardation
- 1:3 with vision impairment
- 50% of children with cerebral palsy
- Long term outcomes
  - Hypertension, diabetes

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## ● Predictors of PTD

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## Predictors of PTD

- Previous PTD (30-40%) recurrence rate
  - Rate of prematurity is inversely related to gestational age
  - 2<sup>nd</sup> trimester loss (60%) risk of recurrence
- Positive cervical fibronectin at 22-24wks
- Short cervix (U/S) at 22-24 weeks

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## Cervical Fibronectin

- Fibronectin found in cervicovaginal secretions after 22 weeks is a marker of disruption of the decidual-chorionic interface
- Has been associated with a six-fold increased risk of preterm birth before 35 weeks and a 14-fold increased risk of preterm birth before 28 weeks

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## Cervical Fetal Fibronectin and PTD

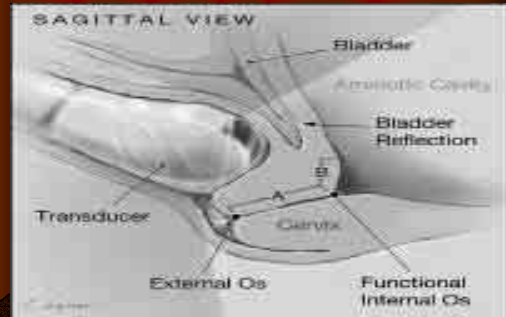
**Table 4.** Risk of Spontaneous Preterm Birth Within Time Intervals in Women With Positive and Negative Cervical Fetal Fibronectin Tests

Gestational age at test (wk)	Fetal fibronectin negative				Fetal fibronectin positive			
	≤7 d	≤14 d	≤21 d	≤28 d	≤7 d	≤14 d	≤21 d	≤28 d
24	0.1	0.4	0.5	0.7	6.1	9.8	12.2	17.1
26	0.1	0.2	0.4	0.8	2.4	6.1	7.3	7.3
28	0.1	0.5	0.9	1.3	0	0	0	3.3
30	0.3	0.6	1.2	2.6	2.5	3.8	10.1	15.2

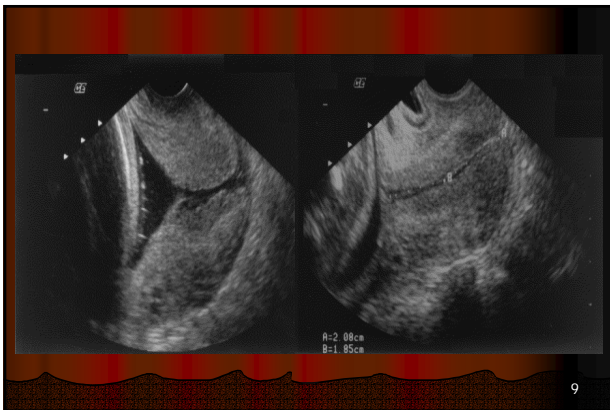
Obstetrics & Gynecology May 1996

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## U/S of the Cervix



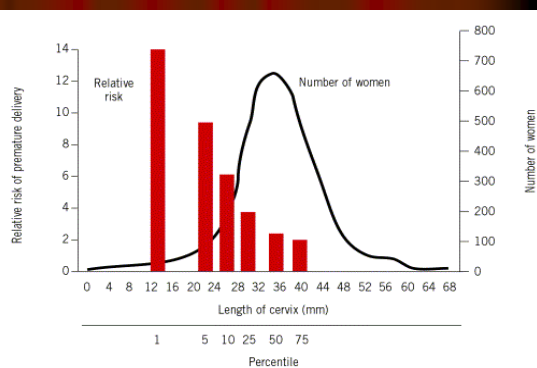
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Cervical effacement begins weeks before delivery, at about 32 w for term births and as early as 16–24 w for preterm births<sup>10</sup>



N Engl J Med. 1996 Feb 29

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## Aims of prediction of PTD

- Identifying risks and applying specific treatment to prevent preterm delivery
- Without having specific treatment may increase the risk to the patient
- Before ordering the test, decide what you going to do with positive results

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## The Role of Cervical U/S and fetal Fibronectin in Clinical Practice

- In women with symptoms of preterm labor
  - If the cervix is <2.5 cm and cervical fetal fibronectin is positive
    - Aggressively manage preterm labor with tocolytic, steroids and antibiotics for gram positive streptococcus
  - If the cervix is >2.5cm and cervical fibronectin is negative
    - No treatment will be required

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## ● Etiology of PTD

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- Inflammation
- Decidual hemorrhage
- Uterine over-distention
- Premature activation of the normal physiologic initiators of labor

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## Infection

- Common in 2<sup>nd</sup> trimester
  - 60% of delivery between 20-30 wks
  - Often chronic infection causes no symptoms or signs except contractions and/or PPROM
  - Ureaplasma, mycoplasma and anaerobes are common organisms causing PTL
  - Metronidazole and erythromycin are the antibiotics of choice

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## Antibiotics and PTD

- Randomized trial of 715 at high risk of preterm delivery (positive fetal fibronectin)
- Gestation 21-26 weeks
- Received either metronidazole (250 mg 8h) and erythromycin (250 mg 6h) or identical placebo for 10 days

Obstet Gynecol 2003;101:847-55

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- No difference was observed in spontaneous preterm birth in antibiotic-compared with placebo-treated women
  - <37 weeks' (CI 0.8-1.7)
  - <35 weeks' (CI 0.54-1.5)
  - <32 weeks' (CI 0.83-4.5)

Obstet Gynecol 2003;101:847-55

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- In asymptomatic women with a positive cervical or vaginal fetal fibronectin test in the late second trimester
- Treatment with metronidazole plus erythromycin does not decrease the incidence of spontaneous preterm delivery

Obstet Gynecol 2003;101:847-55

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## Speculation

- Positive fetal fibronectin is due to inflammation caused by hypoxia/ischemia and not due to infection
- Treatment started too late in the presence of irreversible activation of cytokines/prostaglandin pathways

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- Cervical Incompetence
  - Biological continuum rather than dichotomous
  - Multifactorial
  - Atherosclerosis Model

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## Cervical Incompetence

- The true contribution to PTD is not known
- Previous history is the hallmark of diagnosis
  - Painless 2<sup>nd</sup> trimester rapid delivery

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## Treatment of Cervical Incompetence

- Patient with classical history of cervical incompetence
- Patient with H/O of 2<sup>nd</sup> trimester or early 3<sup>rd</sup> trimester preterm delivery with no classical history

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## MRC/RCOG Randomized Trial

- 1292 women with singleton pregnancies from 12 countries that reported a history of preterm delivery or second-trimester loss (71%) or previous cervical surgery (29%) were randomized early in 2<sup>nd</sup> trimester
- Women with a typical history of cervical insufficiency were not eligible for enrollment in this study
- The frequency of deliveries before 33 weeks for the cerclage group was significantly lower (13% versus 17%,  $P = 0.03$ )

*Br J Obstet Gynecol* 1993;100:516-523

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## Cervical Cerclage

- If the history of previous fetal loss is not classical
- Serial U/S to detect short cervix is common practice
  - short cervix is often a sign of Inflammation rather than incompetent cervix

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## Benefit of Cervical Cerclage in Patient with Short Cervix

- 470 women with short cervix (15 mm or less) at 22-24 weeks were randomized to cervical cerclage or to expectant management
- Primary outcome was delivery before 33 weeks
- Preterm delivery before 33 weeks was similar in both groups, 22% in the cerclage group vs. 26% in the control group, with no significant differences in perinatal or maternal morbidity or mortality

Lancet 2004 Jun 5

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## Speculation

- Short cervix is a sign of cervical inflation and not physical weakness of the cervix
- There are subgroup who had physical weakness of the cervix, however
  - Cerclage was placed too late

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## Cervical Cerclage/Conclusion

- Patient with classical history of cervical incompetence should receive cerclage at 14-16 weeks
- Patient with H not suggestive of cervical incompetence do not need U/S of the cervix and
  - Cerclage is of no value
- Further studies is needed to identify a subgroup with short cervix who will benefit from cerclage
  - Negative cervical fibronectin
  - Negative infection screen

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## ● Use of progesterone to reduce preterm birth

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- Double-blind, placebo-controlled trial at 19 clinical centers
- Documented history of previous spontaneous preterm delivery
- 16 to 20 weeks of gestation
- 310 women in the progesterone group and the 153 women in the placebo group

N Eng J Med 2003 Jun 12

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- Weekly injections of 250 mg of 17 alpha hydroxy Progesterone caproate (17P) or weekly injections of an inert oil placebo
- Injections were continued until delivery or to 36 weeks of gestation

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- 17P significantly reduced the risk of preterm delivery
  - <37 weeks of gestation (36 vs. 55%)
  - <35 weeks of gestation (21 vs. 31%)
  - <32 weeks of gestation (11 vs. 20%)

N Eng J Med 2003 Jun 12

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- Infants of women treated with 17P had significantly lower rates of
  - Necrotizing enterocolitis
  - Intraventricular hemorrhage
  - Need for supplemental oxygen

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### Use of progesterone to reduce preterm birth ACOG 2004

- The ACOG committee on Obstetric Practice recommend that further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors
  - Multiple gestations
  - Short cervical length
  - Positive test results for cervicovaginal fetal fibronectin

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### • Tocolytic Treatment for Preterm Labor

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### Tocolytic

- Magnesium sulphate
- Calcium channel blockers
- Betamimetics
- Prostaglandin inhibitors
- Oxytocin receptor antagonists

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## Cochrane Pregnancy and Childbirth Clinical Trials (2004)

- The Effectiveness of Magnesium Sulphate
- The Effectiveness of Calcium Channel Blockers

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## Effectiveness of Magnesium Sulphate as Tocolytic

- 2000 women were recruited into 23 trials. Only nine trials were rated of high quality
- No difference for the risk of birth within 48 hours of treatment for women given magnesium sulphate compared with controls (CI 0.58-1.25)
- No benefit on the risk of giving birth preterm (<37 or <34 weeks)

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## Effectiveness of Calcium Channel Blockers

- 12 randomized controlled trials (1029 women)
- When compared with any other tocolytic agent (mainly Betamimetics), calcium channel blockers reduced the number of women giving birth within seven days of receiving treatment (CI 0.60 to 0.97) and prior to 34 weeks' gestation (CI 0.69 to 0.99)
- Calcium channel blockers had minimal side effects and newborn had reduced
  - Respiratory distress syndrome
  - Necrotizing enterocolitis
  - Intraventricular hemorrhage

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- When tocolysis is indicated for women in preterm labor, calcium channel blockers are preferable to other tocolytic agents
- Further research should address the effects of different dosage regimens and formulations of calcium channel blockers on maternal and neonatal outcomes

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