Low Birthweight/ Preterm Birth: Issues and Research Needs

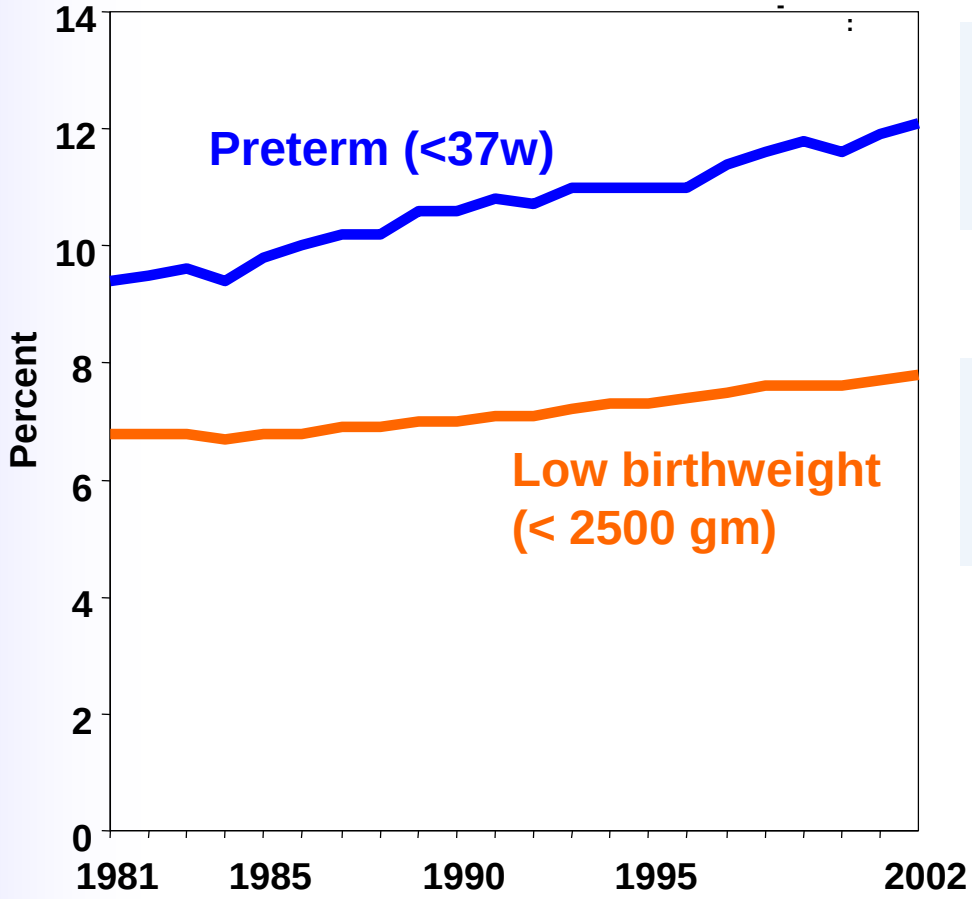
Issues in LBW/Prematurity

- Increasing rates / Incidence
- Consequences
- Etiologies
- Risk Factors
- Markers
- Prevention strategies
- Research needs and focus

Preterm Delivery: A Public Health Priority

- 1 in 8 infants are born preterm
  - 476,000 preterm births each year
- leading cause of hospitalization among pregnant women
- leading cause of death among African-American infants
- associated with developmental disabilities

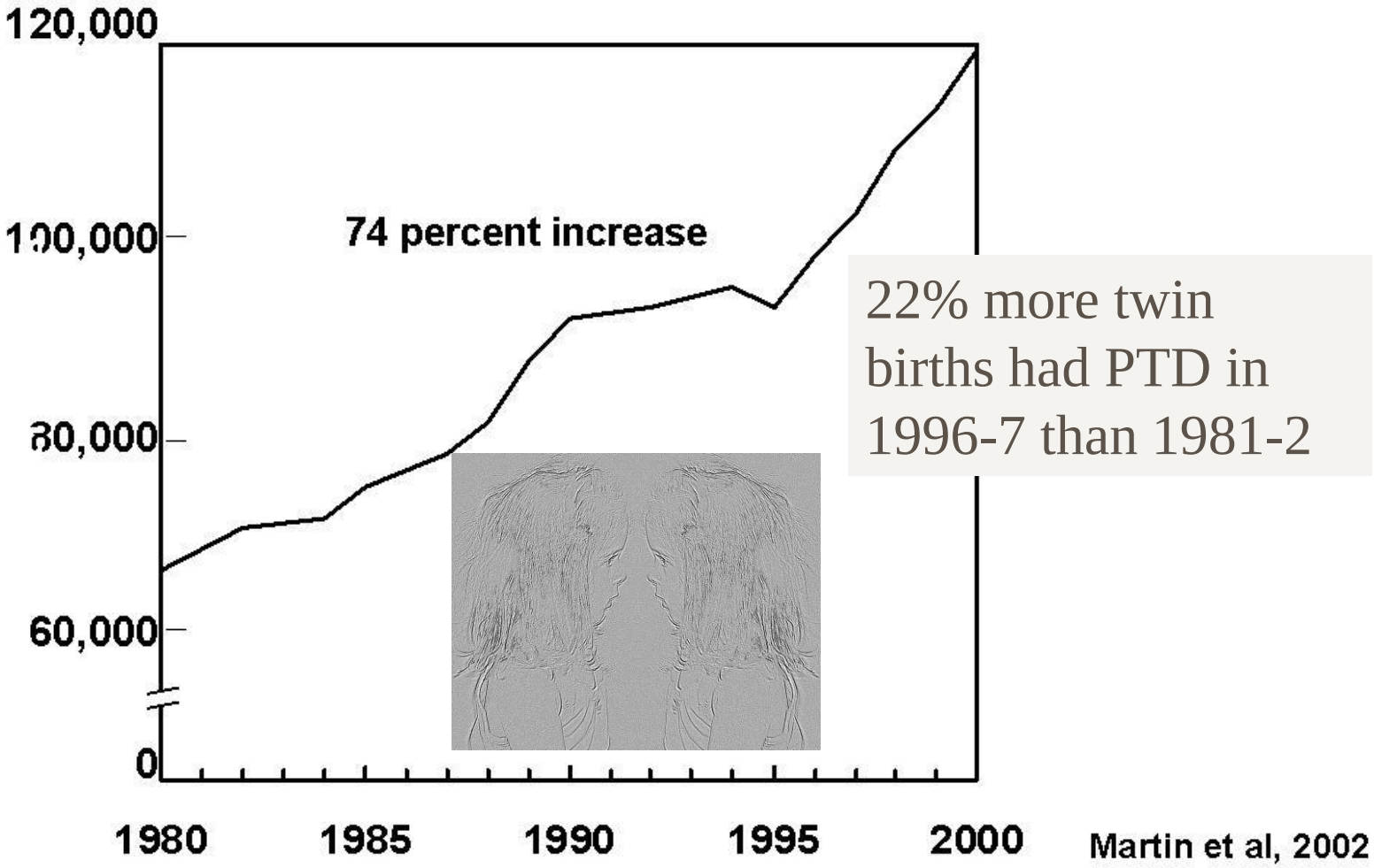
US 1981-2002: Percent Preterm and LBW



- Preterm birth increased 29% since 1981
- LBW increased 15% since 1981

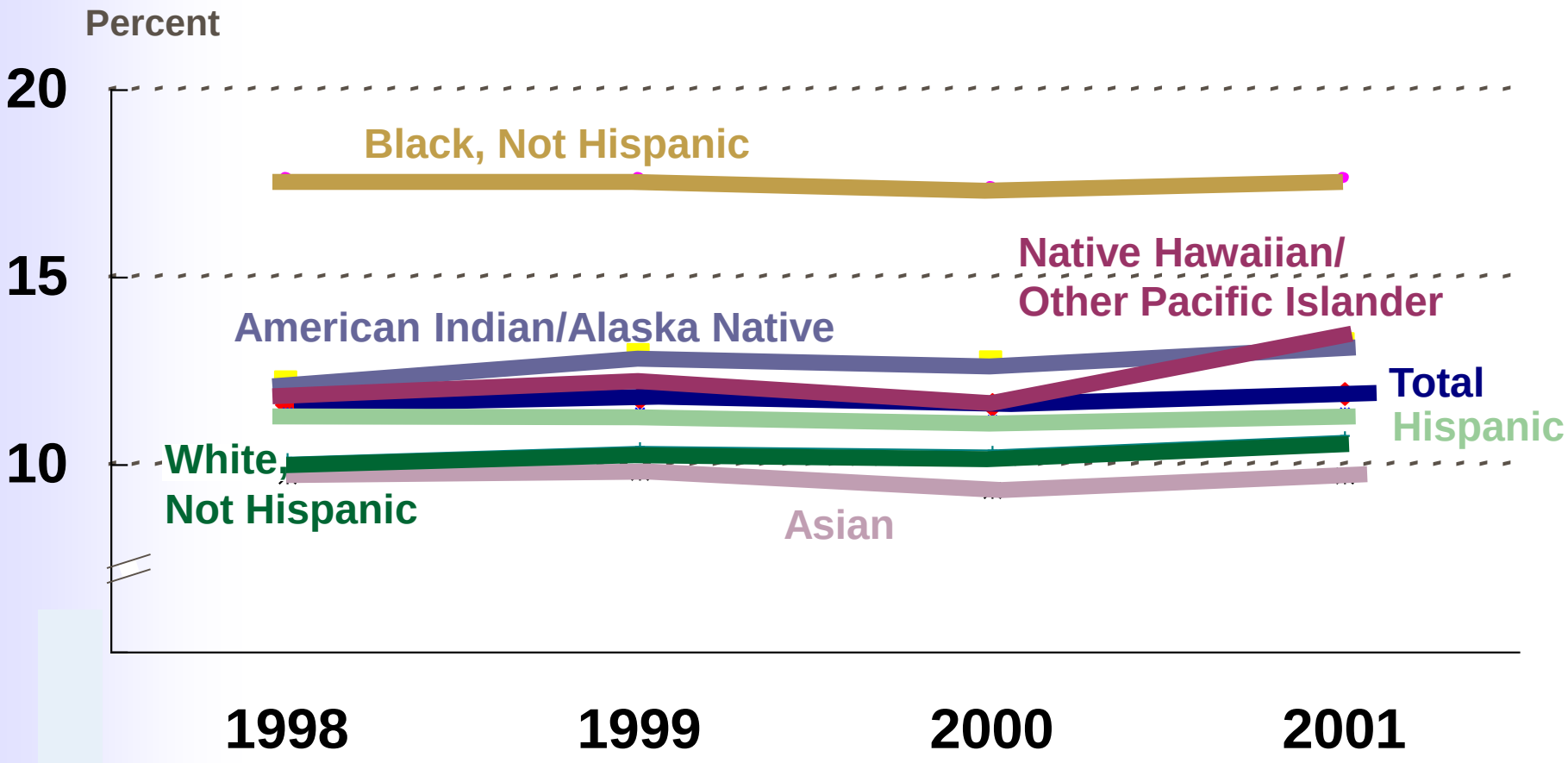
Source: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System

US 1980-2000: Twin Births



22% more twin births had PTD in 1996-7 than 1981-2

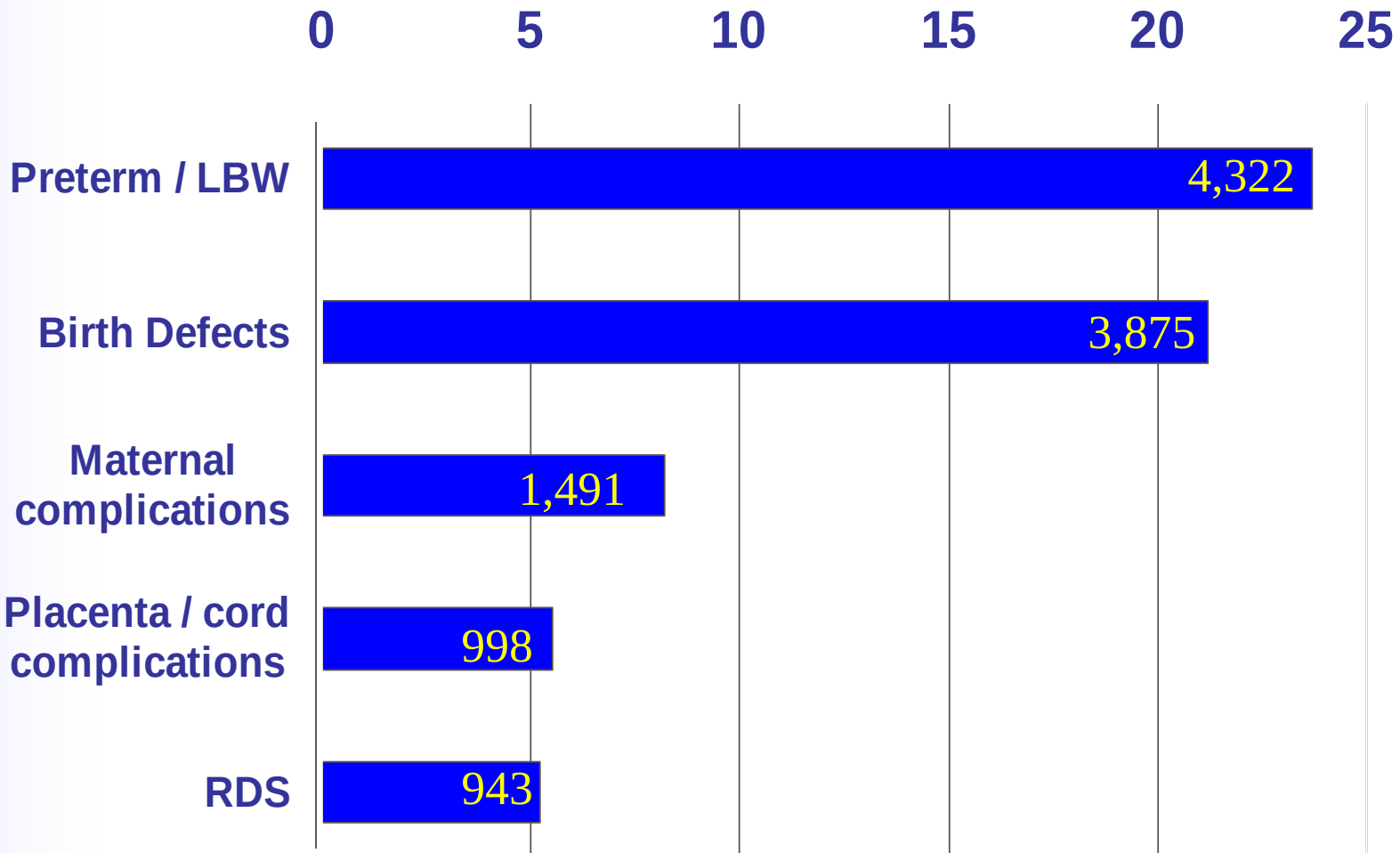
Disparity in preterm birth: race and ethnicity



SOURCE: National Vital Statistics System – Natality NCHS, CDC.

Leading Causes of Neonatal Mortality, 2001

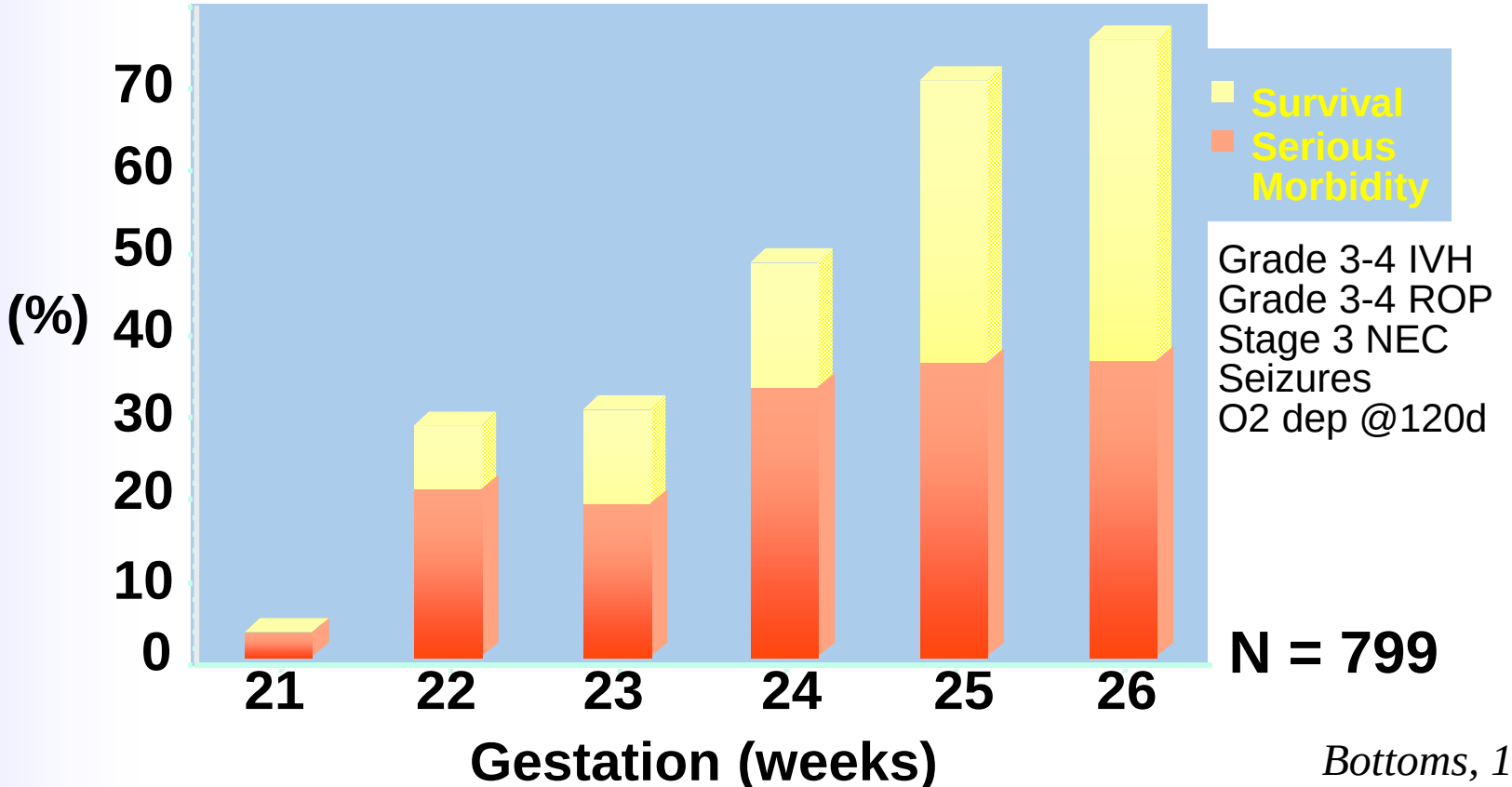
(N / 100,000 live births)



http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_09.pdf Table H. Deaths and percentage of total deaths for the 10 leading causes of neonatal and postneonatal deaths: United States, 2001

Preterm Birth: Outcome

Accounts for
- 1 out of 5 children with mental retardation
- 1 out of 3 children with vision impairment
- Almost half of children with cerebral palsy



Bottoms, 1995

Preterm Birth: Long Term Outcome

- *For the baby:*
  - Increased risk for cardiovascular disease (MI, stroke, hypertension) as an adult
  - Increased risk for diabetes as an adult
  - Possible increase in cancer risk
- *For the mother:*
  - Increased risk for subsequent preterm delivery

Predictors of Preterm Birth

Importance of identification of markers

- To initiate risk-specific treatment
- To define a population and evaluate an intervention/therapy
- To learn mechanisms of preterm delivery

Risk factors for PTD

- Multiple gestation
- Previous preterm birth
- Uterine/cervical abnormalities
- Shortened cervical length
- African American race
- Age (<17, >35)

Medical risk factors:

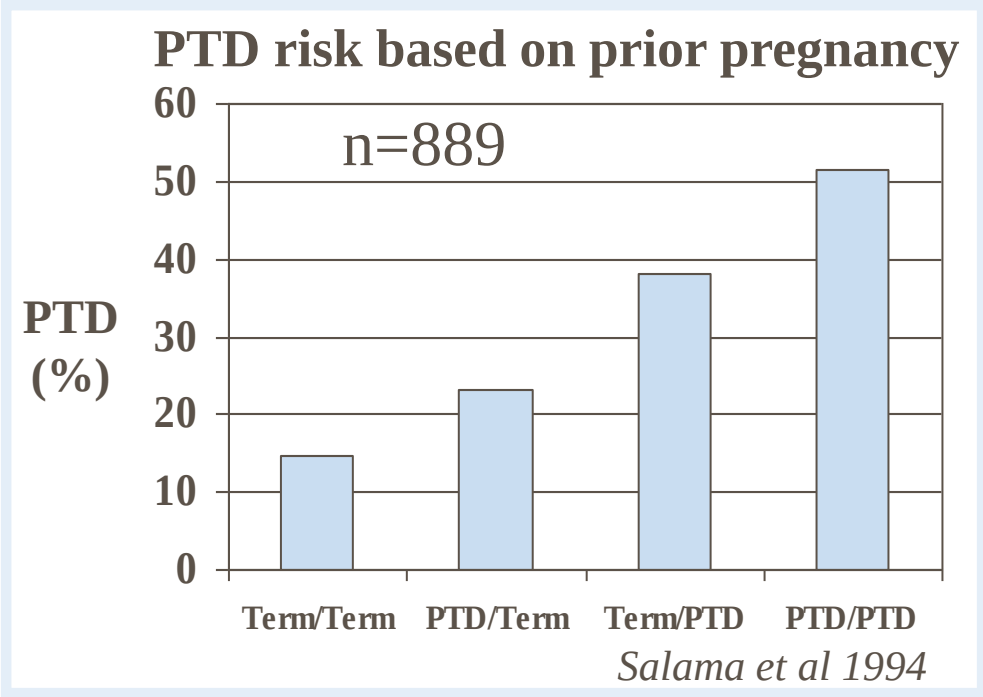
- PROM
- Infections (UTI, vaginal infections, STD)
- High blood pressure
- Diabetes
- Clotting disorders (thrombophilia)
- Maternal weight (underweight or obesity)
- Short time period between pregnancies
- Certain birth defects
- Vaginal bleeding

Lifestyle risk factors:

- Late or no prenatal care
- Smoking
- Drinking alcohol
- Using illegal drugs
- Domestic violence
- Lack of social support
- High levels of stress
- Long working hours
- Low income

Women “at risk” for PTD

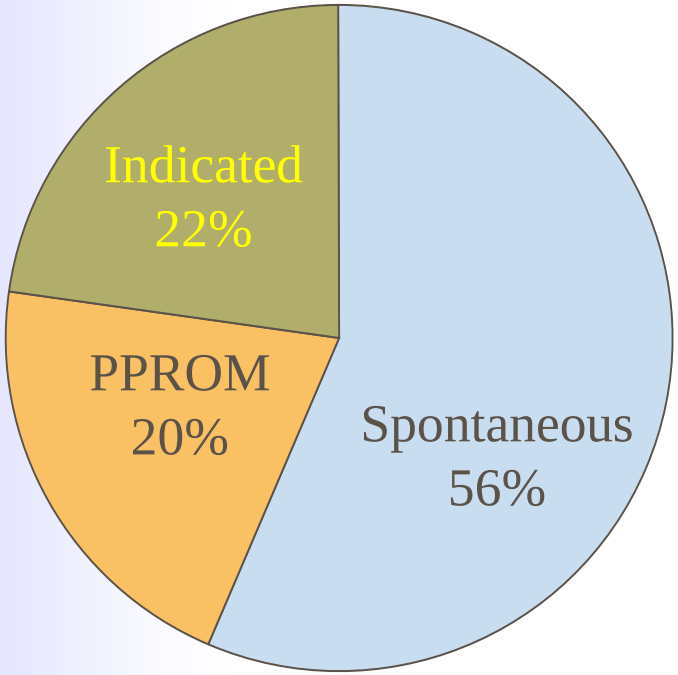
- Prior spontaneous PTD
- Multiple gestation
- Uterine anomaly
- Cervical incompetence
- Socioeconomic status
- Biochemical markers (e.g. FFN)
- Shortened cervical length
- Vaginal / cervical infections /inflammation



Risk Scoring Systems and PTD

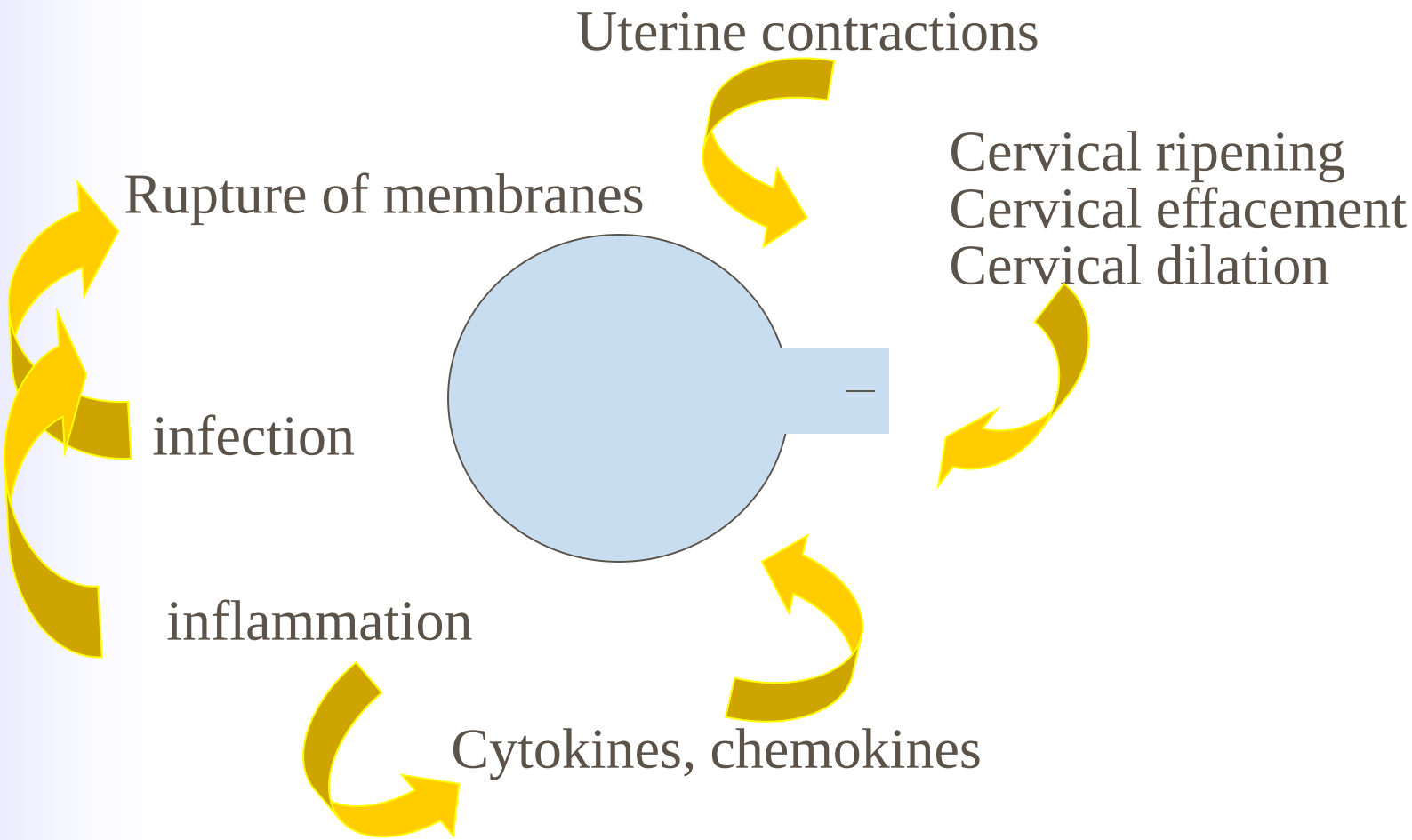
- Low sensitivity, high false positive rates
- Majority of women who have PTD are from a low risk group
- Identification of high risk status has not led to improvement in outcome
- Importance of effective intervention for risk factor / marker

Categories of Preterm Births

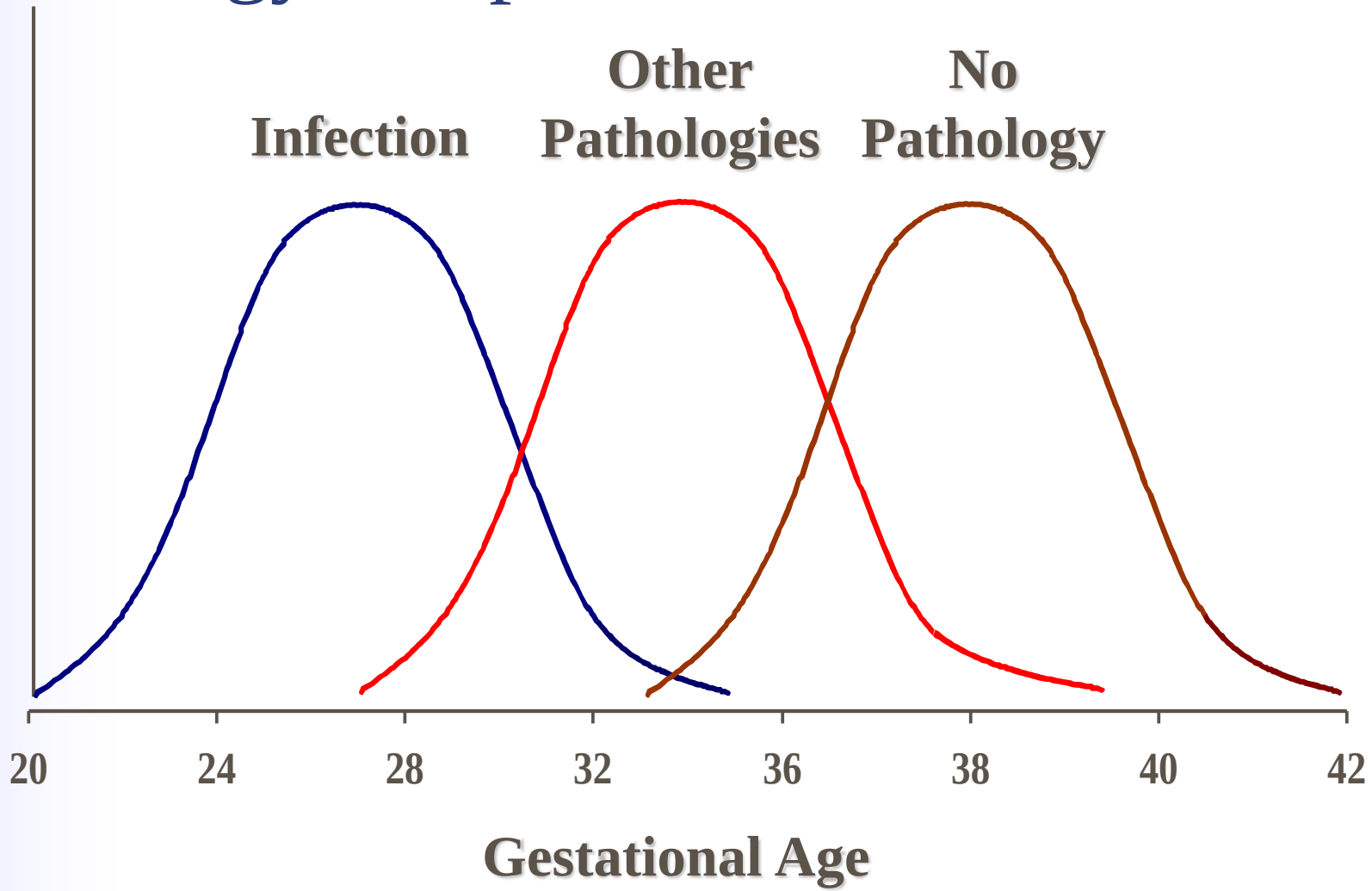


- Spontaneous preterm labor (56%)
- Preterm premature rupture of the fetal membranes (20%)
- Preterm deliveries indicated for fetal or maternal reasons (22%)

Spontaneous Preterm Delivery: Mechanisms



Etiology of Spontaneous PTB



Infection and sPTD

- Evidence supports infection cause of PTD:
  - Clinical chorioamnionitis
  - Subclinical chorioamnionitis

Bacteria associated with prematurity

- Ureaplasma
- Mycoplasma
- Gardnerella
- Mobiluncus
- Peptostreptococcus
- Bacteroides

Antibiotics: PTL & intact membranes

Study	Antibiotic	N	Delayed Delivery	Improved Infant Outcome
MacGregor, 1986	Erythromycin	17	**Yes**	No
Morales, 1988	Erythromycin, Ampicillin	150	**Yes**	No
Winkler, 1988	Erythromycin	19	**Yes**	-
Newton, 1989	Erythromycin / Ampicillin	95	No	No
MacGregor, 1991	Clindamycin	103	**Yes**	No
McCaul, 1992	Ampicillin	40	No	No
Romero, 1993	Ampicillin / Amoxicillin / Erythromycin	275	No	No
Cox, 1995	Ampicillin / Amoxicillin	78	No	No
Gordon, 1995	Ceftizoximine	117	No	No
Norman, 1994	Metronidazole / Ampicillin	81	**Yes**	**Yes**
Svare, 1997	Metronidazole / Ampicillin	110	**Yes**	?
Oracle Trial	Erythromycin or Amoxicillin		No	No

Antibiotics & BV

- RCT metronidazole +BV with hx prior sPTD

  PTD 18% v 39%, p<.05 *Morales et al 1994*

- RCT metronidazole+erythromycin in high risk women, +BV

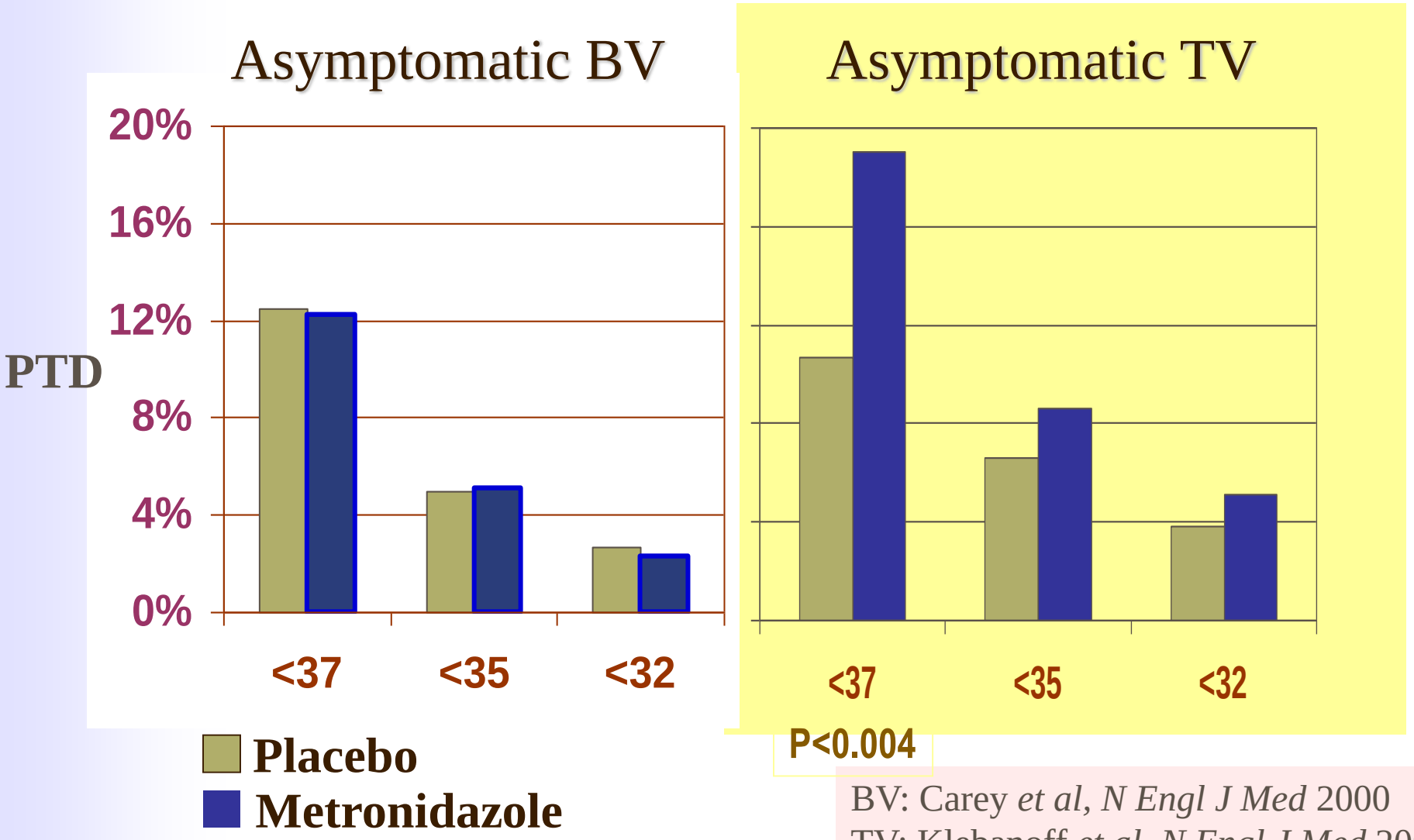
  PTD 23% v 37%, p<.001 *Hauth et al 1994*

NICHD: MFMU BV/TV Trial

- **Aim:** To establish whether metronidazole therapy will reduce the risk of PTD in women with asymptomatic bacterial vaginosis or trichomonas vaginalis
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** <24 wks, BV or TV positive
- **Intervention:** Four doses of 2g metronidazole or placebo
- **Primary outcome:** delivery at < 37 weeks'
- **Sample:** BV: 1900 pregnant women (950/group)
  TV: 1900 pregnant women (950/group)

BV: Carey *et al, N Engl J Med* 2000
TV: Klebanoff *et al, N Engl J Med* 2001

Rates of Preterm Birth



BV: Carey *et al*, *N Engl J Med* 2000
TV: Klebanoff *et al*, *N Engl J Med* 2001

BV/TV trials

- TV trial stopped by DSMC after interim analysis found increased PTD in metronidazole group
- Effectiveness of treatment
  - BV: 78% negative for BV
  - TV: 93% negative for trichonomiasis

BV: Carey *et al*, *N Engl J Med* 2000
TV: Klebanoff *et al*, *N Engl J Med* 2001

BV/TV trials: Conclusions

- Treatment of *asymptomatic*
  - BV does not reduce PTD or adverse perinatal outcomes
  - TV **increased** the risk of PTD

Results from these trials changed the practice of indiscriminate use of antibiotics in pregnancy

BV: Carey *et al*, *N Engl J Med* 2000
TV: Klebanoff *et al*, *N Engl J Med* 2001

Fetal Fibronectin (FFN)

- Membrane protein localized to area between fetus and mother
- Role in implantation and placentation
- When detected in cervical or vaginal secretions of asymptomatic women is associated with >50-fold increased risk in PTD<28wks
- Intrauterine infection may disrupt fetal membranes and result in release of FFN

Goldenberg *et al*, *Am J Obstet Gynecol* 2000

Antibiotics for FFN+ to prevent PTD

- **Aim:** To establish whether metronidazole therapy will reduce the risk of PTD in FFN+ women
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** FFN+ at 21-25 wks
- **Intervention:** 10 day course metronidazole and erythromycin or placebo
- **Primary outcome:** delivery at < 37 weeks'
- **Sample:** 715 pregnant women
- **Findings:** No improvement in sPTD or nn outcome

Andrews *et al*, *Obstet Gynecol* 2003

Infection, Antibiotics and PTD

	Antibiotics Helpful
Infection with intact membranes	No
+BV, high-risk women	Yes
+BV, low risk women	No
+TV	No
+FFN	No

Home Uterine Contraction Monitoring to Prevent Preterm Delivery

- 2422 insured, at-risk women
- Intervention: weekly phone call, daily phone call, or HUCM system
- HUCM & Daily Call groups: higher Rx
- No changes in PTD, birthweight, cx dilation

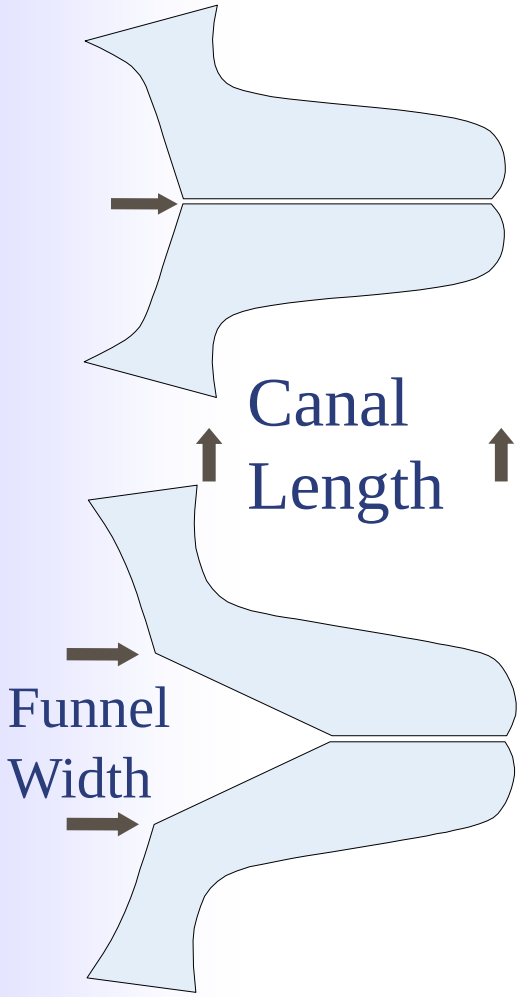
Dyson et al NEJM 1998

The HUAM Prediction Study

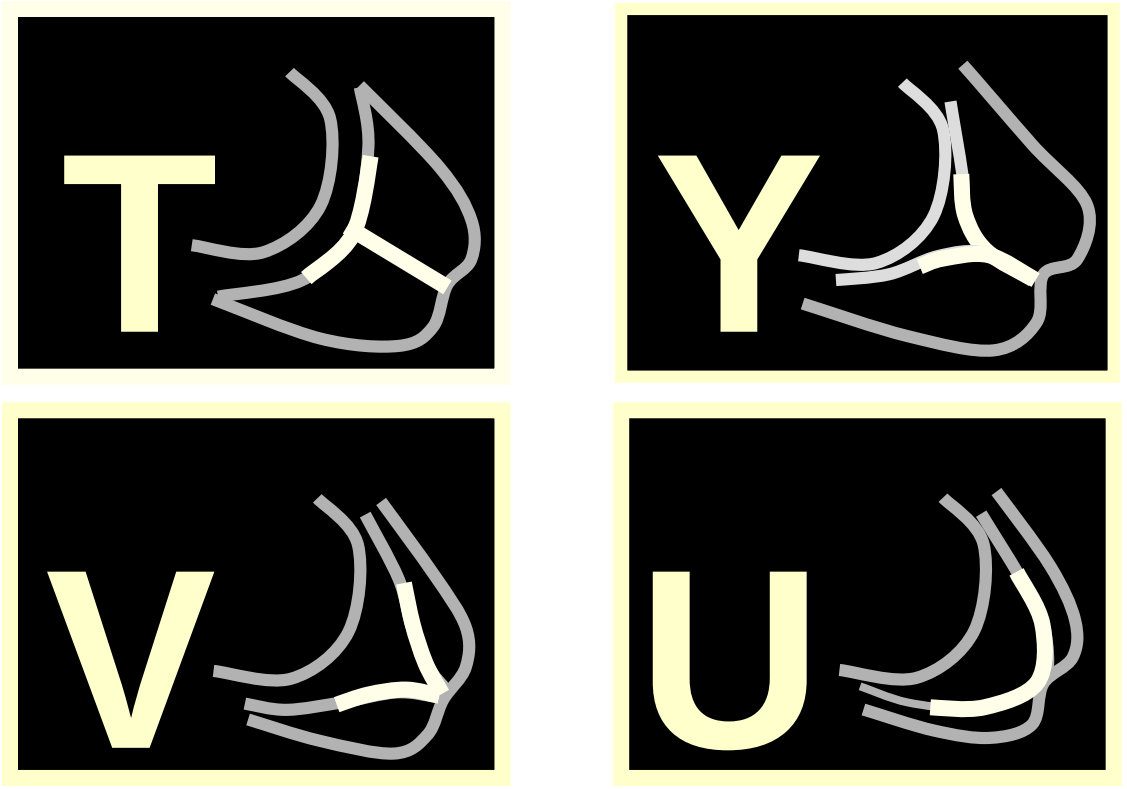
- Blinded monitoring of Women w/ Risk of PTD
  - Contraction frequency was related to risk of PTD
  - Contractions predicted PTD poorly
    - *Sensitivity = 9.3%* for ≥ 4 Contractions / hr
    - *PPV = 26.7%* to predict birth < 35 weeks
- Contractions are common in pregnancy
- Increased frequency in women who will have PTD is too small to be clinically useful
- Contractions occur late in process

Iams et al NEJM 2002

Shortened cervix

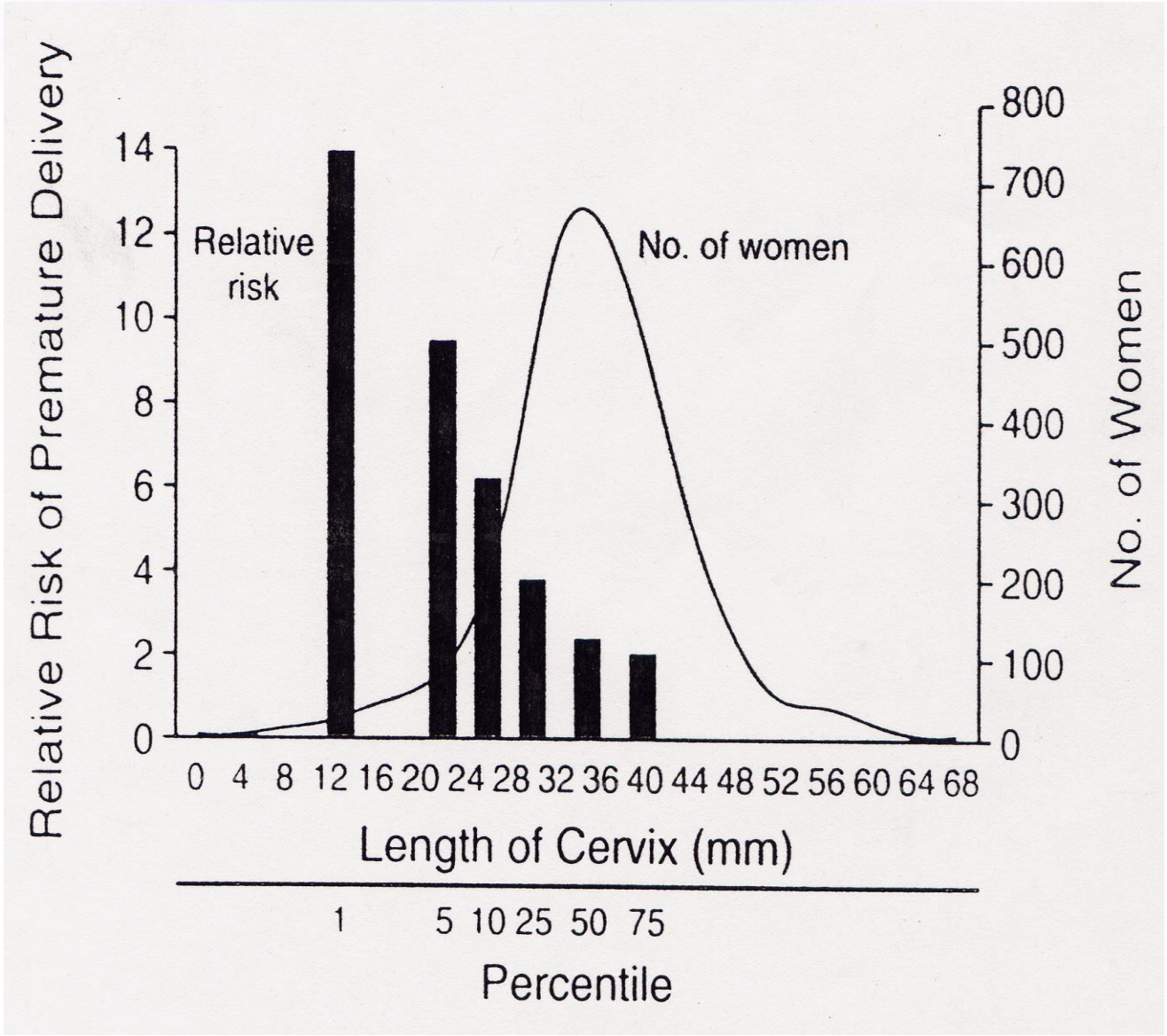


Mechanism of Effacement:



Zilanti M, et al: JUM 1995

Relative Risk of SPTD < 35 wks by % of cervical length at 24 wks



Iams et al, NEJM 1996

Cervical length

- Follows a Bell curve
- Risk of PTD increases as cervical length decreases across entire range of length
- Cervical changes are same at all GA

Limited studies available to determine effectiveness of Cerclage to prevent PTD in women with PTD

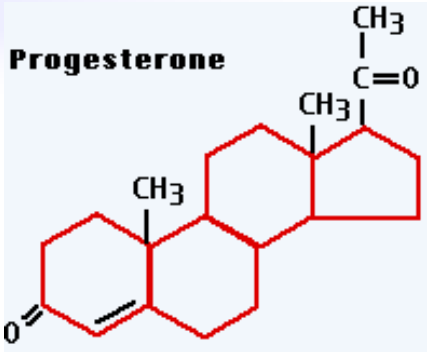
Berghella et al AJOG 1999
Althuisius et al AJOG 2000
Rust et al AJOG 2001
Newman et al AJOG 2002

Cerclage: Meta-Analysis & Reviews

- Owen et al *AJOG* 2003:
  - "Results are inconclusive"
- Odibo et al *Ob Gyn Survey* 2003:
  - "Trend toward less PTD but not NN mortality"
- Bachmann et al *Acta Obstet Gynecol* 2003
  - "Significant reduction in PTD < 34 weeks"
- Belej-Rak et al *AJOG* 2003r
  - "No support for cerclage to reduce PTD"

To *et al*, *Lancet* 2004; 363:1849-53
RCT of 253 women with CL <15 mm: cerclage vs none
No difference PTD <33 wks (22% vs 26%, p=0.4)

Progesterone



- Steroid hormone
- Progesterone is a small hydrophobic molecule.
- Diffuses freely through the plasma membrane of all cells
- In **target cells**, (endometrium)
  - becomes tightly bound to a cytoplasmic protein the **progesterone receptor**
  - the complex of receptor-hormone moves into nucleus
  - binds to a progesterone response element (a specific sequence of DNA in the promoters of certain genes that is needed to turn those genes on/off). The complex of progesterone with its receptor forms a transcription factor.

Actions of Progesterone on the Myometrium

- Decreases conduction of contractions
- Increases threshold for stimulation
- Decreases spontaneous activity
- Decreases number of oxytocin receptors
- *Prevents formation of gap junctions*

Early Trials of Progesterone

Johnson JWC. *NEJM* 1975;293:675-680

- 43 patients (recur Ab or PTD)
- Rx: 17P or placebo
- 41% of placebo group delivered <36 wks
- 100% of treated group delivered >36 wks

Hauth JC. *Am J Obstet Gynecol* 1983;146:187

- 168 pregnant women in the military
- Rx: 17P or placebo
- Low birth weight infants:
  - 7.5% in treated subjects
  - 9.0% in placebo subjects

Meta-analysis of 17P in pregnancy

- 5 trials: high risk women with 17P
- Pooled analysis of results showed:
  - Reduction in rates of preterm birth
    Odds ratio 0.50, 95% CI: 0.30-0.85
  - Reduction in rates of low birthweight
    Odds ratio 0.46, 95% CI: 0.27-0.80

Keirse MJNC. *Brit J Obstet Gynecol* 1990;97:149

Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study

- University of Sao Paulo Medical School, Brazil
- RCT double-blind, placebo controlled
- 1996-2001
- Rx: daily Progesterone (100 mg) vs placebo as vaginal suppository from 24 – 34 wks

Da Fonseca *et al*
AJOG 2003;188:419-24

Methods

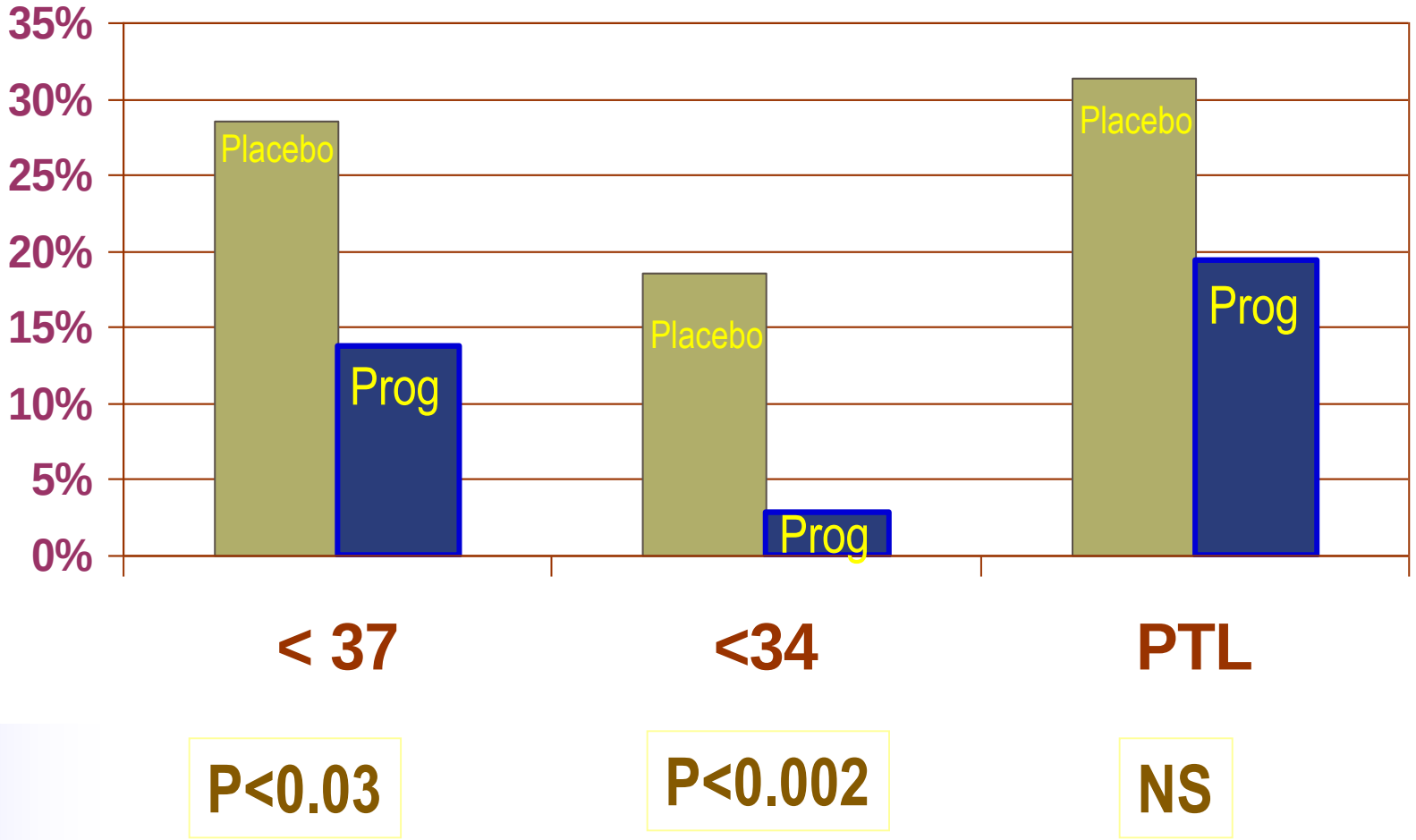
- 157 high risk singleton pregnancies, 15(9.5%) lost to follow-up;
  - Prior sPTD (avg 33 wks)
  - Prophylactic cervical cerclage
  - Uterine malformation
- Analyzed remaining 142
  - 70 placebo
  - 72 progesterone

Da Fonseca *et al*
AJOG 2003;188:419-24

Characteristics

	Prog	Placebo
Qualifying delivery (wks)	33.3	33.4
Maternal age (yrs)	27.6	26.8
Caucasian	68%	71%
Risk Factor		
Prior PTD	90%	97%
Uterine malformation	5.6%	1.4%
Incompetent cervix	4.1%	1.4%

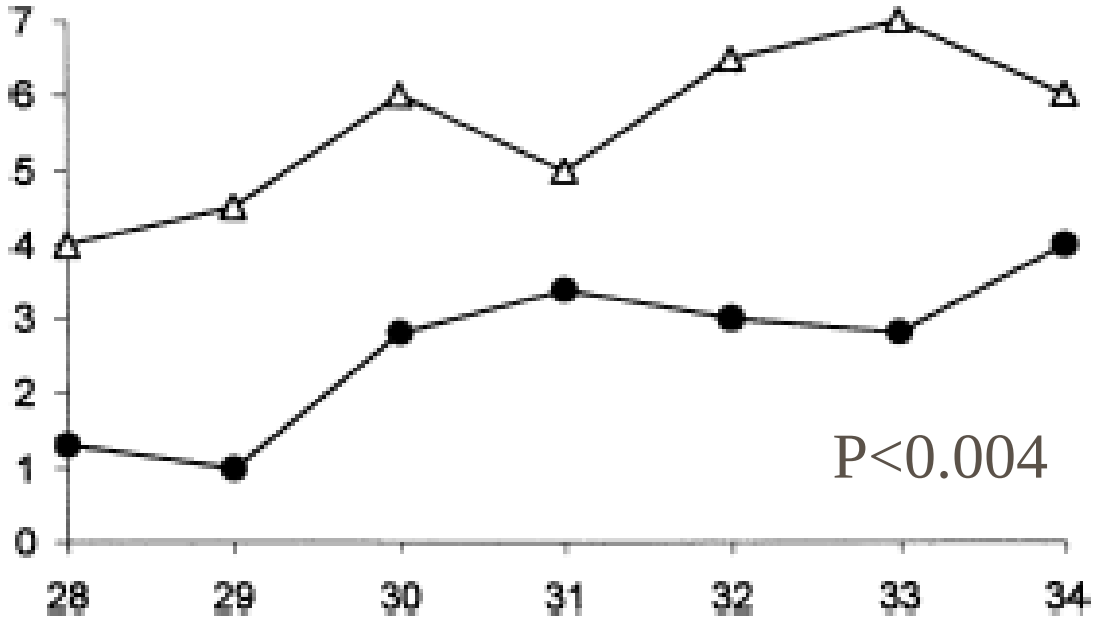
Rates of Preterm Birth



Da Fonseca *et al*
AJOG 2003;188:419-24

Uterine contraction frequency

1 hr monitoring/wk



Da Fonseca *et al*
AJOG 2003;188:419-24

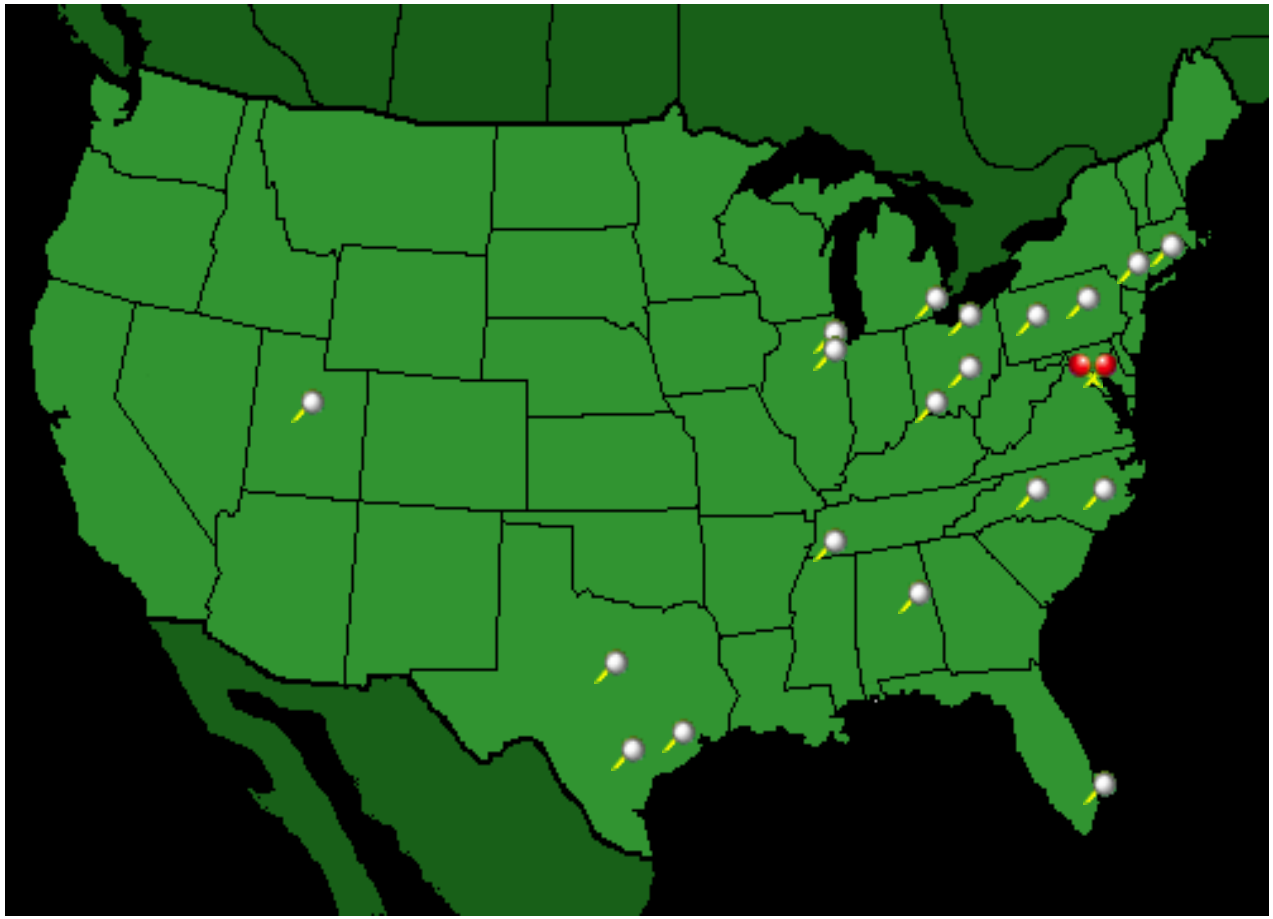
Findings

- Progesterone
  - prevented preterm delivery in women with prior PTD, especially <34 wk
  - reduced the frequency of uterine contractions

Da Fonseca *et al*
AJOG 2003;188:419-24

Progesterone trial for the prevention of preterm delivery in high-risk women

NICHD Maternal Fetal Medicine Units Network



Meis et al, NEJM, 2003

NICHD: MFMU Progesterone Trial

- **Aim:** To establish if weekly progesterone injections in women with prior spontaneous preterm delivery (sPTD) reduces the risk of PTD
- **Design:** double-masked, placebo-controlled trial
- **Eligibility criteria:** singleton pregnancy 16-20 wks with documented previous sPTD
- **Intervention:** progesterone or placebo
- **Primary outcome:** delivery at < 37 weeks'
- **Sample:** 463 pregnant women

Meis *et al, N Engl J Med* 2003

19 Centers enrolled women with:

- Documented history of spontaneous preterm birth at 20^0 to 36^6 weeks' gestation in a previous pregnancy
- Gestational age at entry of 15-20^3 weeks confirmed by ultrasound
- Singleton gestation, with no major fetal anomalies

Meis *et al, N Engl J Med* 2003

Randomization & follow-up

- Given a trial injection of the placebo inert oil, and asked to return in 1 week
- At next visit,(16^0 - 20^6 wks) randomly assigned by a central randomization scheme, to receive injection of 250 mg 17P or a placebo inert oil
- The women returned for weekly injections of 17P or placebo until 37 weeks or delivery

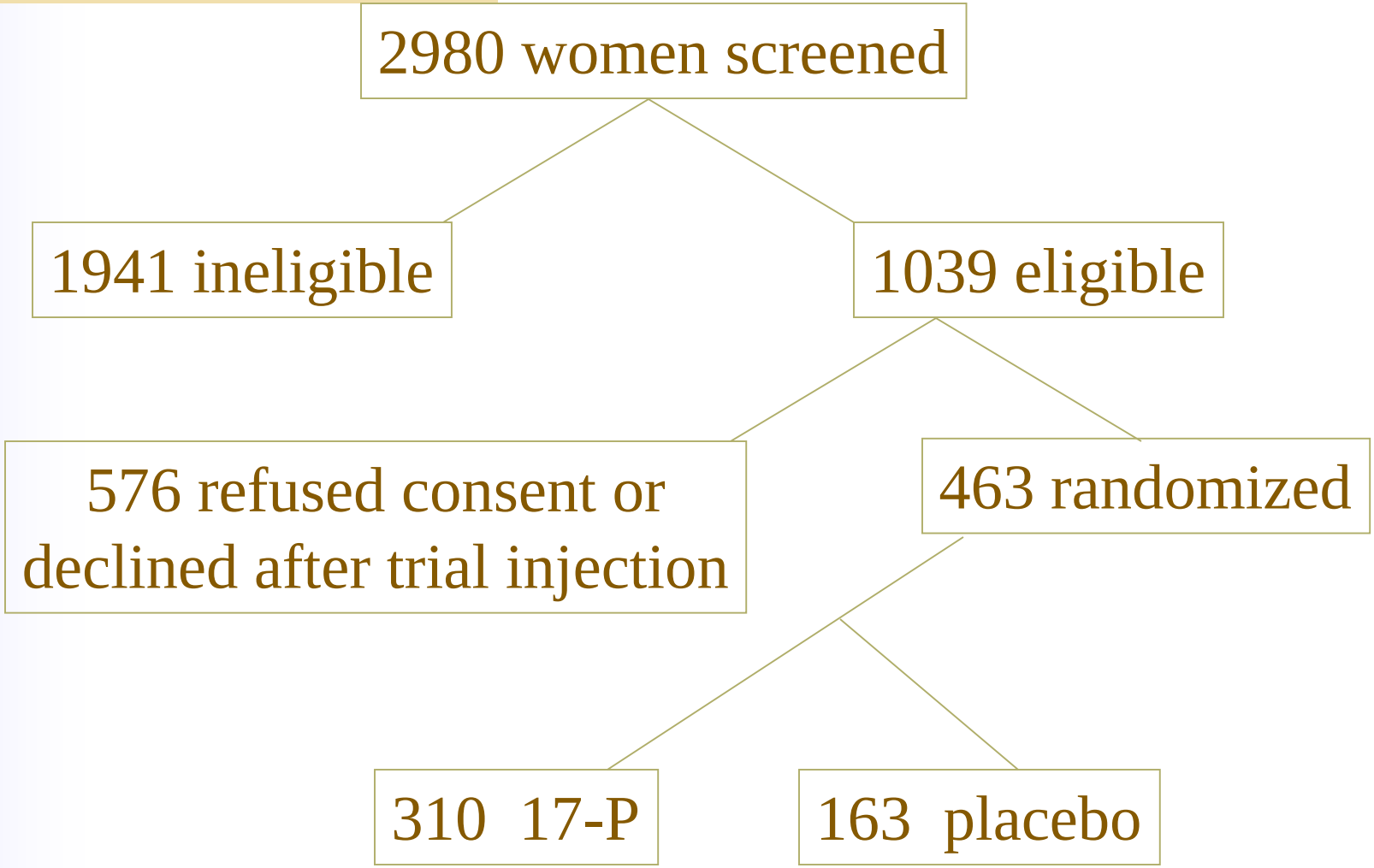
Meis *et al*, *N Engl J Med* 2003

Review by Data and Safety Monitoring Committee

- Interim analysis was performed after 351 subjects had delivered
- Analysis showed positive effect for the primary outcome
- Enrollment of new subjects was halted when 463 subjects randomized

Meis *et al, N Engl J Med* 2003

Screening & Randomization

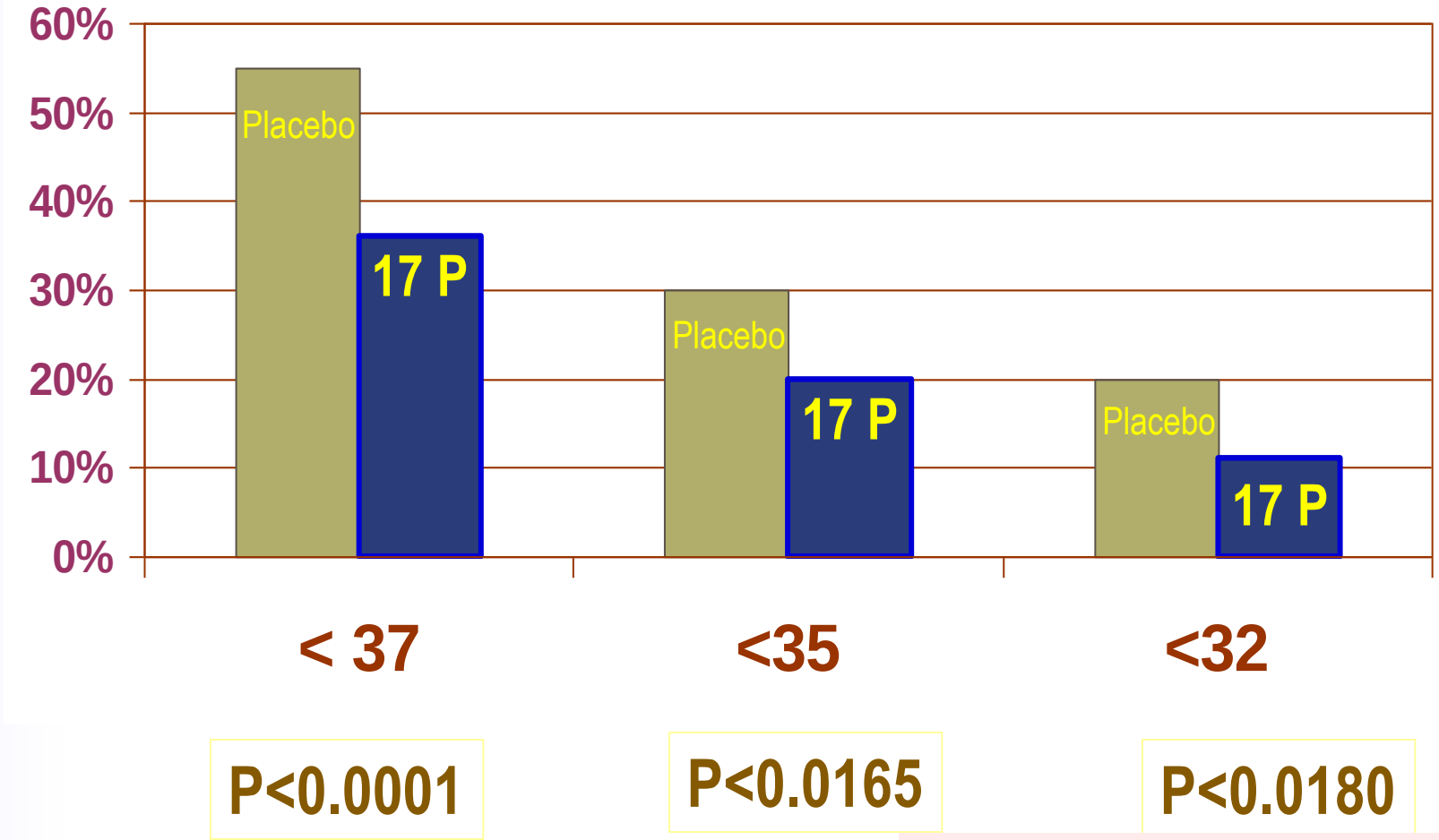


Characteristics

	17-P	Placebo
Qualifying delivery (wks)	30.5	31.3
Maternal age (yrs)	26.0	26.5
Married	51%	46%
African American	59%	58%
Mean BMI	26.9	25.9
Smoking	22%	19%

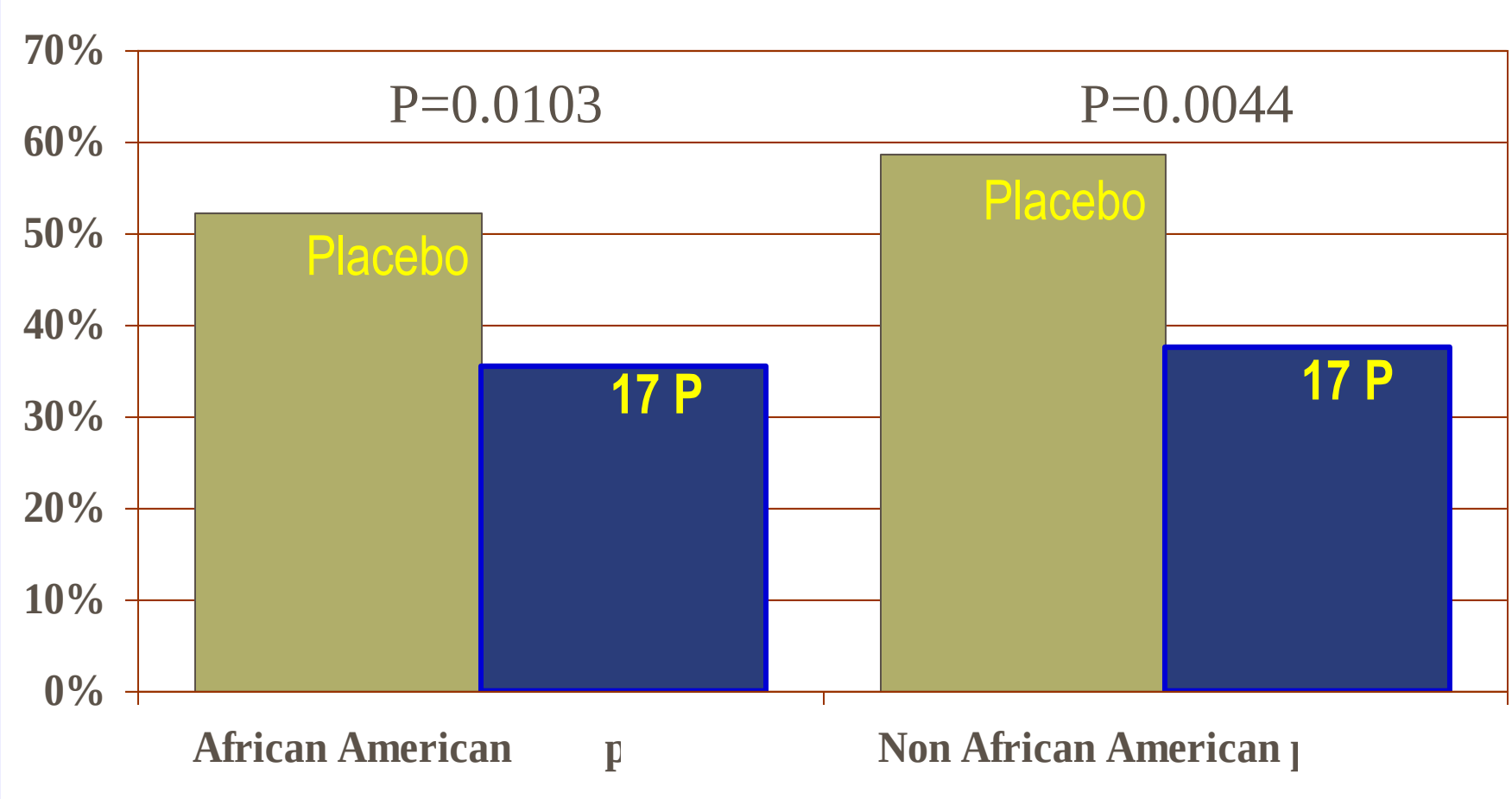
Meis *et al, N Engl J Med* 2003

Progesterone: Rates of Preterm Birth



Meis *et al, N Engl J Med* 2003

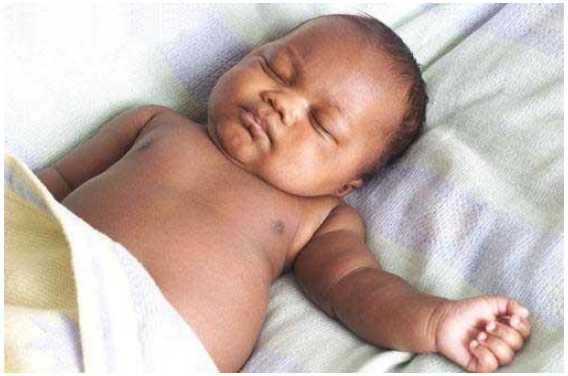
Progesterone Results: Ethnic Group



Meis *et al, N Engl J Med* 2003

Effectiveness of Progesterone

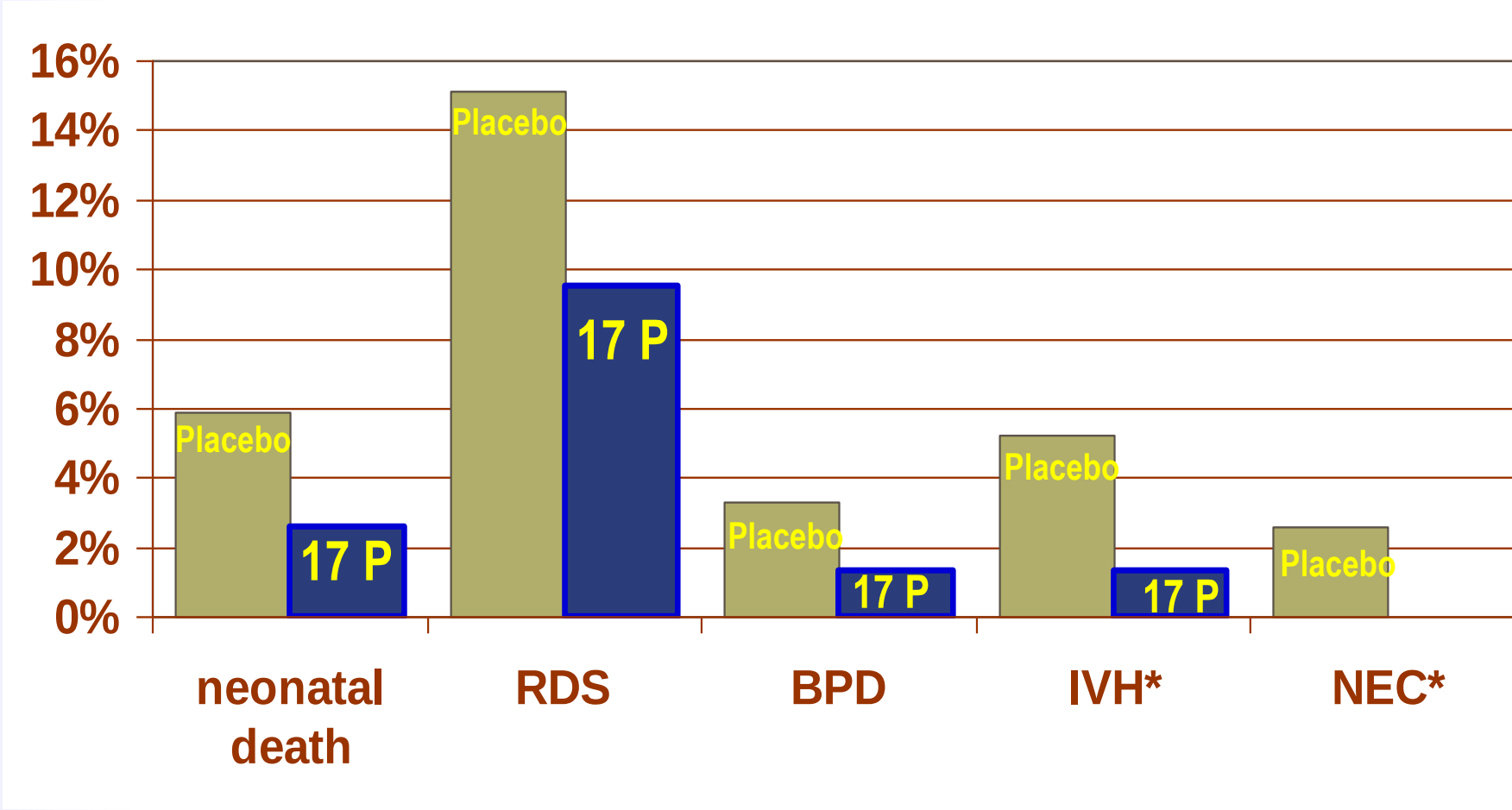
- 5-6 women with a previous sPTB would need to be treated to prevent one birth <37 weeks



- 12 women with a previous sPTB birth would need to be treated to prevent one birth <32 weeks

Meis *et al, N Engl J Med* 2003

Progesterone prevents neonatal complications



Meis *et al, N Engl J Med* 2003

Compliance and Side Effects

- Compliance with the weekly injections was excellent
- 91.5% of the women received their injections at the scheduled time
- Side effects were minor and were similar in the 17P and placebo groups

Meis *et al, N Engl J Med* 2003

Progesterone prevents recurrent preterm delivery

- Weekly injections of progesterone prevented recurrent preterm birth and improved the neonatal outcome for pregnancies at risk
- Effective in preventing very early as well as later preterm birth
- Effective in both African American and Non-African American women

Meis *et al, N Engl J Med* 2003

ACOG Committee Opinion:
Use of Progesterone to Reduce Preterm Birth

- Recent studies support progesterone supplementation reduces PTD in select group of women (prior sPTD < 37 wks)
- Further studies are needed to evaluate the use of progesterone in patients with other high-risk conditions (multiple gestation, short cervical length, positive FFN)
- Recommend restricting progesterone use to prevent PTD for women with prior sPTD

Obstet Gynecol 2003;102:1115-6

Putting it all together

Should women "at risk" be started on progesterone?

- PTD etiologies: heterogeneous
- Limited (if any) ability to predict PTD
- Many women "at risk"
  - Demographic characteristics
  - Behavioral factors
  - Obstetric history
- Certainly not all will benefit from progesterone

Should women “at risk” be started on progesterone?

- Prior to da Fonseca and Meis trials – no evidence based research supporting preventative treatment for women to prevent PTD
- Overall, limited data available for at risk conditions
- There is evidence to support progesterone treatment ***for women with prior sPTD***

Women "at risk" for PTD

- Prior spontaneous PTD
- ~~Multiple gestation~~
- ~~Uterine anomaly~~
- ~~Cervical incompetence~~
- ~~Socioeconomic status~~
- ~~Biochemical markers (e.g. FFN)~~
- ~~Shortened cervical length~~
- ~~Vaginal / cervical infections /inflammation~~

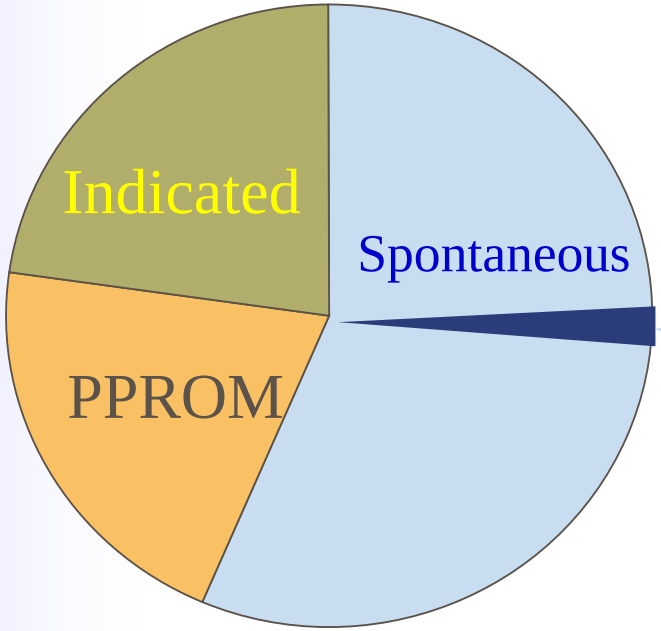
Medical risk factors:

- PROM
- Infections (UTI, vaginal infections, STD)
- High blood pressure
- Diabetes
- Clotting disorders (thrombophilia)
- Maternal weight (underweight or obesity)
- Short time period between pregnancies
- Certain birth defects
- Vaginal bleeding

Lifestyle risk factors:

- Late or no prenatal care
- Smoking
- Drinking alcohol
- Using illegal drugs
- Domestic violence
- Lack of social support
- High levels of stress
- Long working hours
- Low income

LBW/Prematurity: Research Needs



Prior spontaneous PTD

- Only one risk factor
- Small % of all PTD

Major initiatives into:

-Understanding the cause(s)

-Methods of prevention and treatment in pregnant women

-Optimal management/treatment of neonates

Major Research Advances

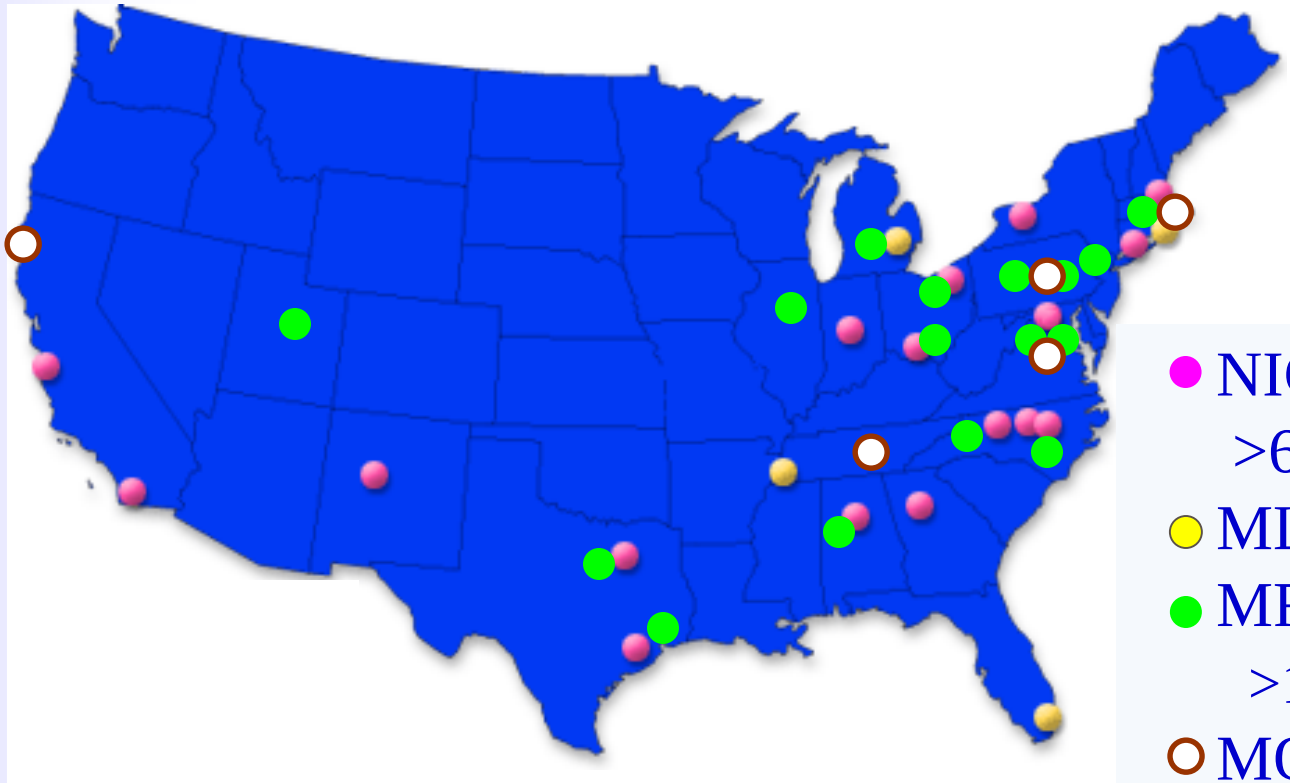
- Markers, management and prevention of PTD
  - Markers: history, FFN, cervical length
  - Management: antenatal steroids, antibiotics & PPROM
  - Prevention: Progesterone
- Management of preterm neonate
  - Inhaled nitric oxide
  - Optimal nutrition for preterm neonate

Prematurity/LBW Research needs:

- Major focus:
  - Prevention
  - Treatment
  - Management of preterm neonates
- Mechanisms:
  - Researcher initiated grants
  - Targeted requests
  - NIH Multicenter Networks
  - Education

Mechanism
Pathophysiology
Genetics
Disparity

NICHD Networks



- NICU Network sites
  >60,000 babies/yr
- MLS Network sites
- MFMU sites
  >120,000 deliveries/yr
- MOMs sites

- High risk pregnancies: PTD/LBW prevention and management
- Management of the preterm and LBW neonate
- Long term outcome of prematurity and LBW

LBW/Prematurity: Research Needs

- Investigator initiated grants
- Trials in NICHD clinical networks
  - Identify markers
  - Identify treatment
  - Identify preventative therapies
  - Identify optimal management
- Long-term follow-up
- National Children's Study

National Children's Study

- Long term study of environmental influences on children' health and development
- Children's Health Act, 2000 authorized NICHD Director to collaboratively
  - "…conduct a national longitudinal study of environmental influences (including physical, chemical, biological, and psychosocial) on children's health and development"
- Follow 100,000 children during prenatal development, birth, childhood into adulthood
- Would allow major scientific initiatives to gain understanding, management and treatment of preterm birth

Prematurity Prevention: A Public Health Priority

- 1 in 8 infants are born preterm (476,000 preterm births / year)
- Leading cause of neonatal death
- Major cause of long-term morbidity
- Impacts adult health

LBW/Prematurity Prevention

To reduce:

- LBW, Preterm labor and delivery
- Risk of pregnancy related deaths and complications related to pregnancy
- Infant mortality caused by LBW/prematurity

Critical need for:

- Answers to major research questions
- Clinical trials and longitudinal data
- Long term follow-up

The goal: healthy children and mothers…