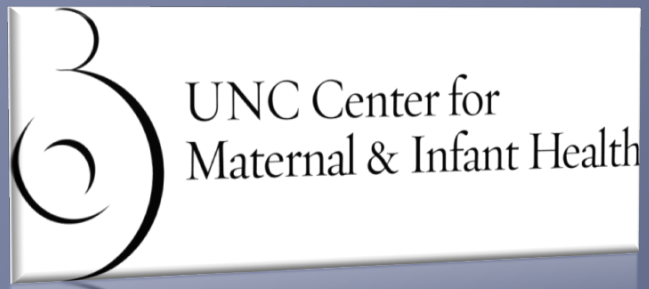

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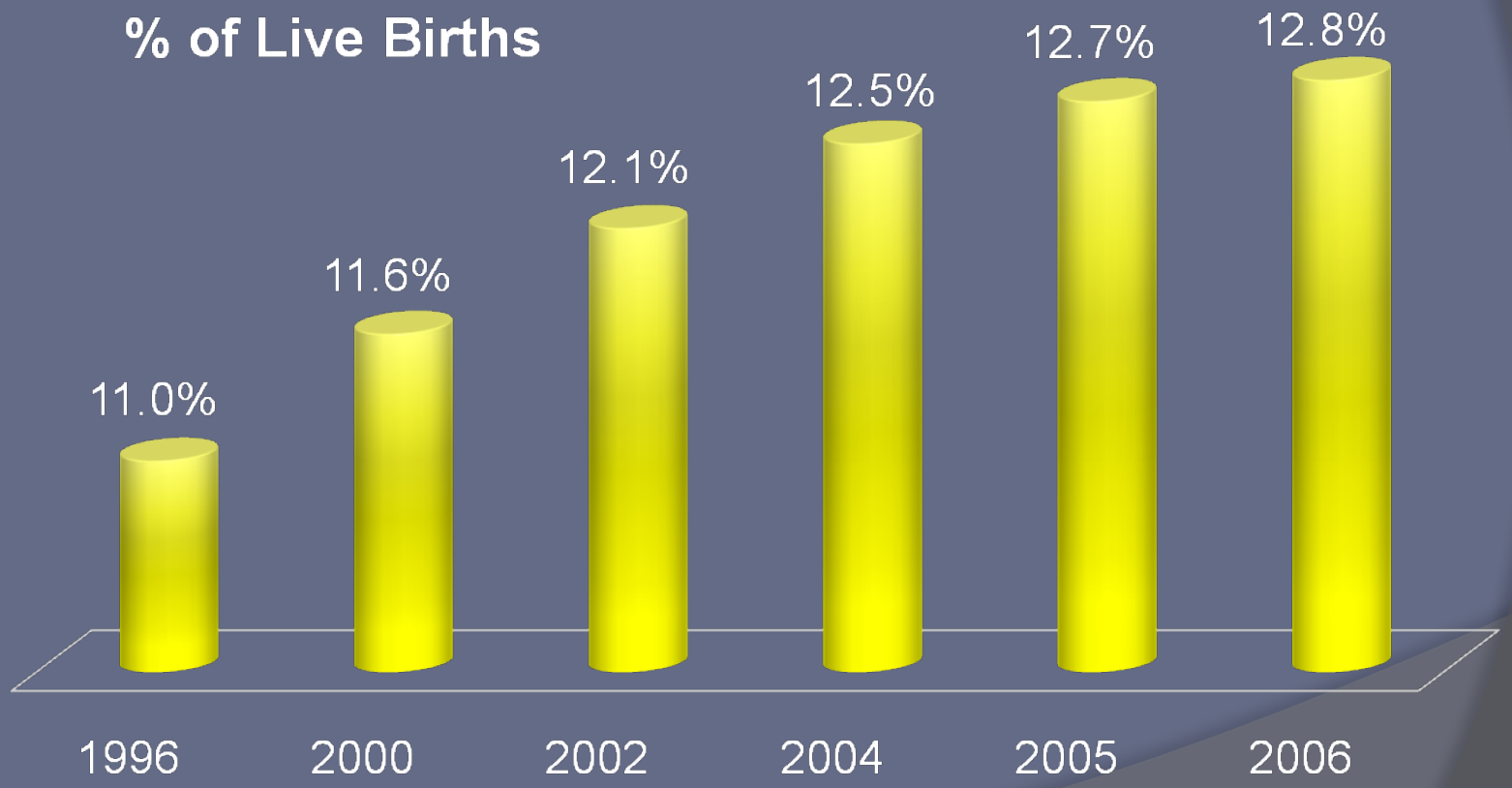
UPDATE ON PROGESTERONE AND PREVENTION OF PRETERM BIRTH

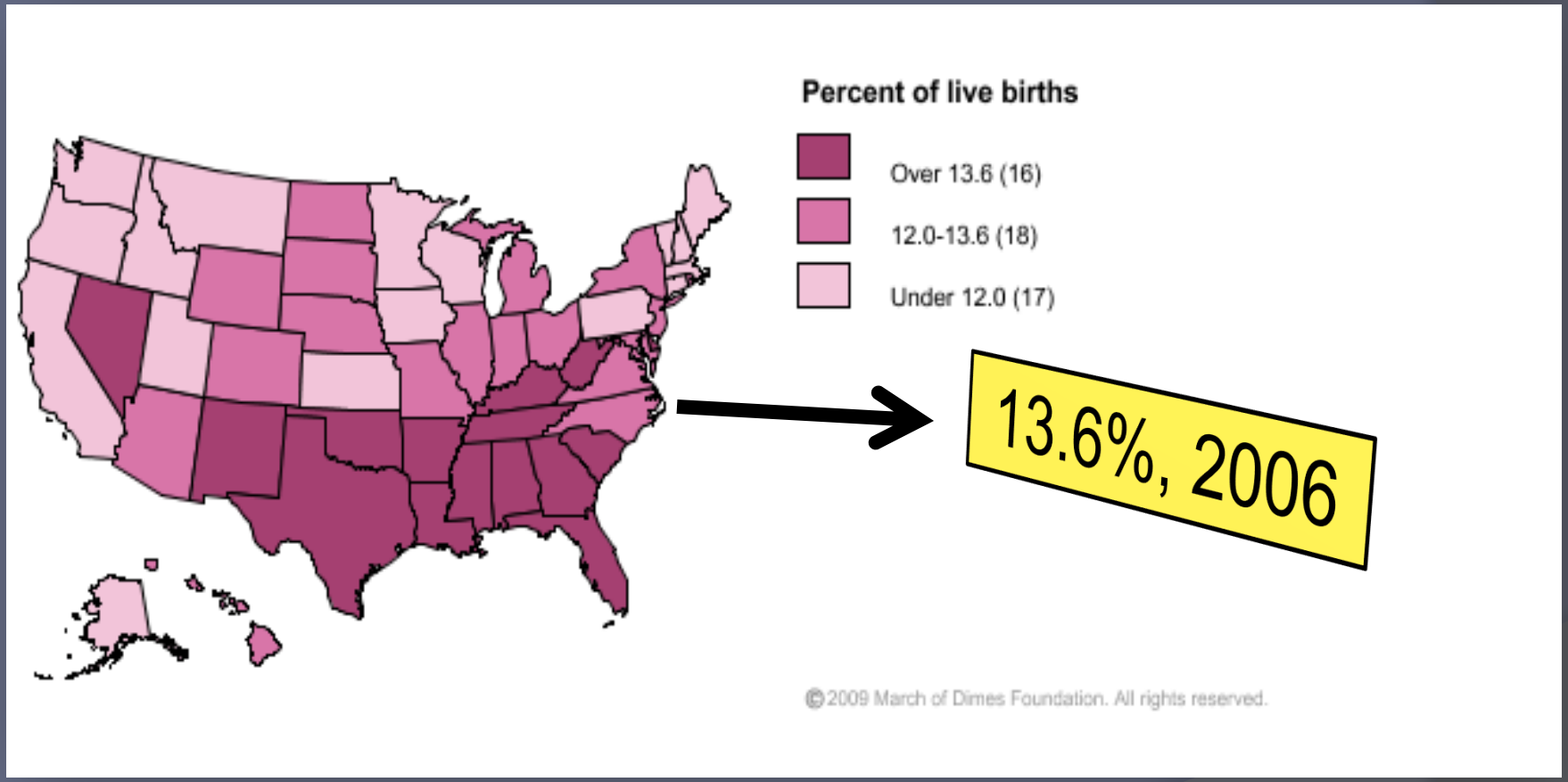
Scope of the problem - US

- Preterm Birth – delivery <37 weeks EGA



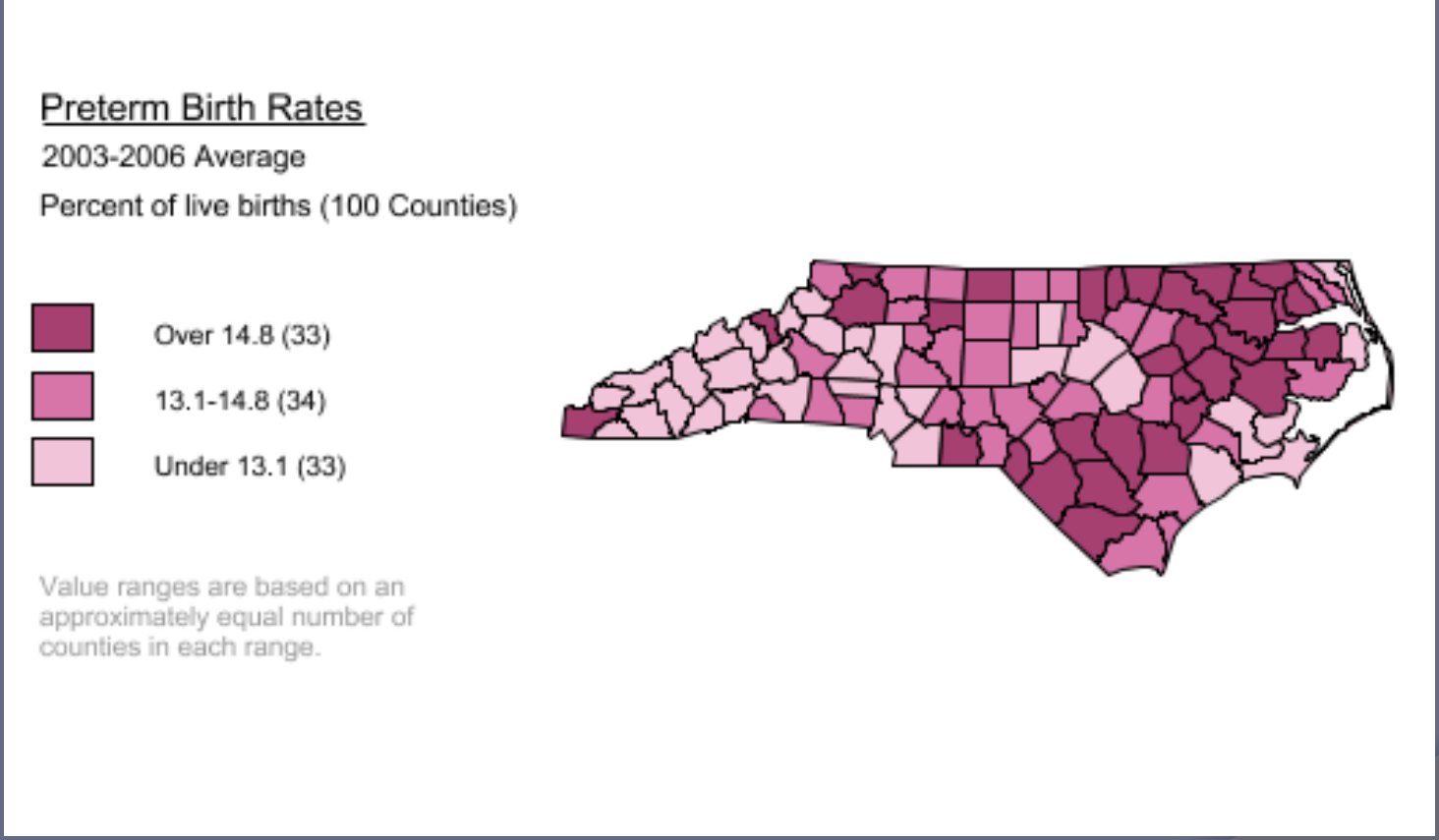
National Center for Health Statistics. Retrieved October 15, 2009, from www.marchofdimes.com/peristats.

Scope of the Problem - NC



National Center for Health Statistics. Retrieved October 15, 2009, from www.marchofdimes.com/peristats.

Scope of the Problem - NC



National Center for Health Statistics. Retrieved October 15, 2009, from www.marchofdimes.com/peristats.

Implications of PTB

- Leading cause
  - neonatal morbidity and mortality
  - long term morbidity
    - cerebral palsy
    - developmental delay

Risk factors for preterm birth

- Prior PTB ***
- Multiple gestation
- Short cervical length
- Low maternal BMI
- African American
- Maternal age
- Smoking

Interventions to prevent PTB

- Prenatal care
  - Social support
- Lifestyle changes
  - Smoking cessation
  - Improved nutrition
- Cerclage
- Infections
- Home uterine activity monitoring
- Tocolytic medications

Trials of acute care of PTL show little benefit in prevention of PTB

Progesterone for prevention of PTB

- Small trials in 1970's and 80's
- Suggested
  - Reduction in preterm birth
- Variable dosing
  - IM
  - Vaginal
- Variable populations

Early progesterone trials

- 5 trials in high risk women with 17P vs. placebo
- Overall risks of:
  - **preterm birth**
    - **OR 0.50, 95% CI: 0.30-0.85**
  - **low birth weight**
    - **OR 0.46, 95% CI: 0.27-0.80**
- **No difference in morbidity/mortality**

40-50% reduction

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

Why may progesterone work?

- Functional prog withdrawal stimulates labor
  - Increase PR-A/PR-B expression
  - Decrease progesterone receptors
- Progesterone as anti-inflammatory
- Reduce myometrial gap junctions
  - Decrease conduction of contractions
- Reduces threshold for contractions

NICHD/MFMU
17 α-Hydroxyprogesterone Caproate

The NEW ENGLAND JOURNAL of MEDICINE

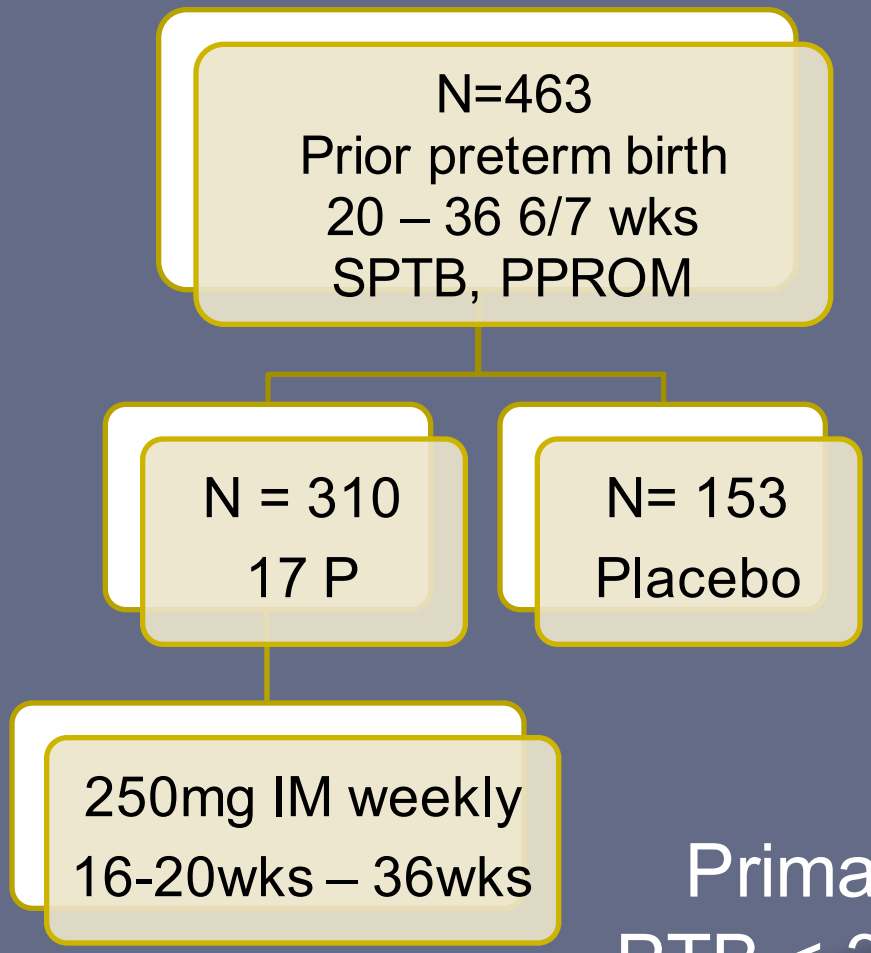
ESTABLISHED IN 1812 JUNE 12, 2003 VOL. 348 NO. 24

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

Paul J. Meis, M.D., Mark Klebanoff, M.D., Elizabeth Thom, Ph.D., Mitchell P. Dombrowski, M.D., Baha Sibai, M.D., Atef H. Moawad, M.D., Catherine Y. Spong, M.D., John C. Hauth, M.D., Menachem Miodovnik, M.D., Michael W. Varner, M.D., Kenneth J. Leveno, M.D., Steve N. Caritis, M.D., Jay D. Iams, M.D., Ronald J. Wapner, M.D., Deborah Conway, M.D., Mary J. O'Sullivan, M.D., Marshall Carpenter, M.D., Brian Mercer, M.D., Susan M. Ramin, M.D., John M. Thorp, M.D., and Alan M. Peaceman, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

New England Journal of Medicine, 2003; 348 (24)

17P – NICHD (Meis, 2003, NEJM)



Primary outcome:
PTB < 37 weeks EGA

17-P NICHD trial (Meis, 2003, NEJM)

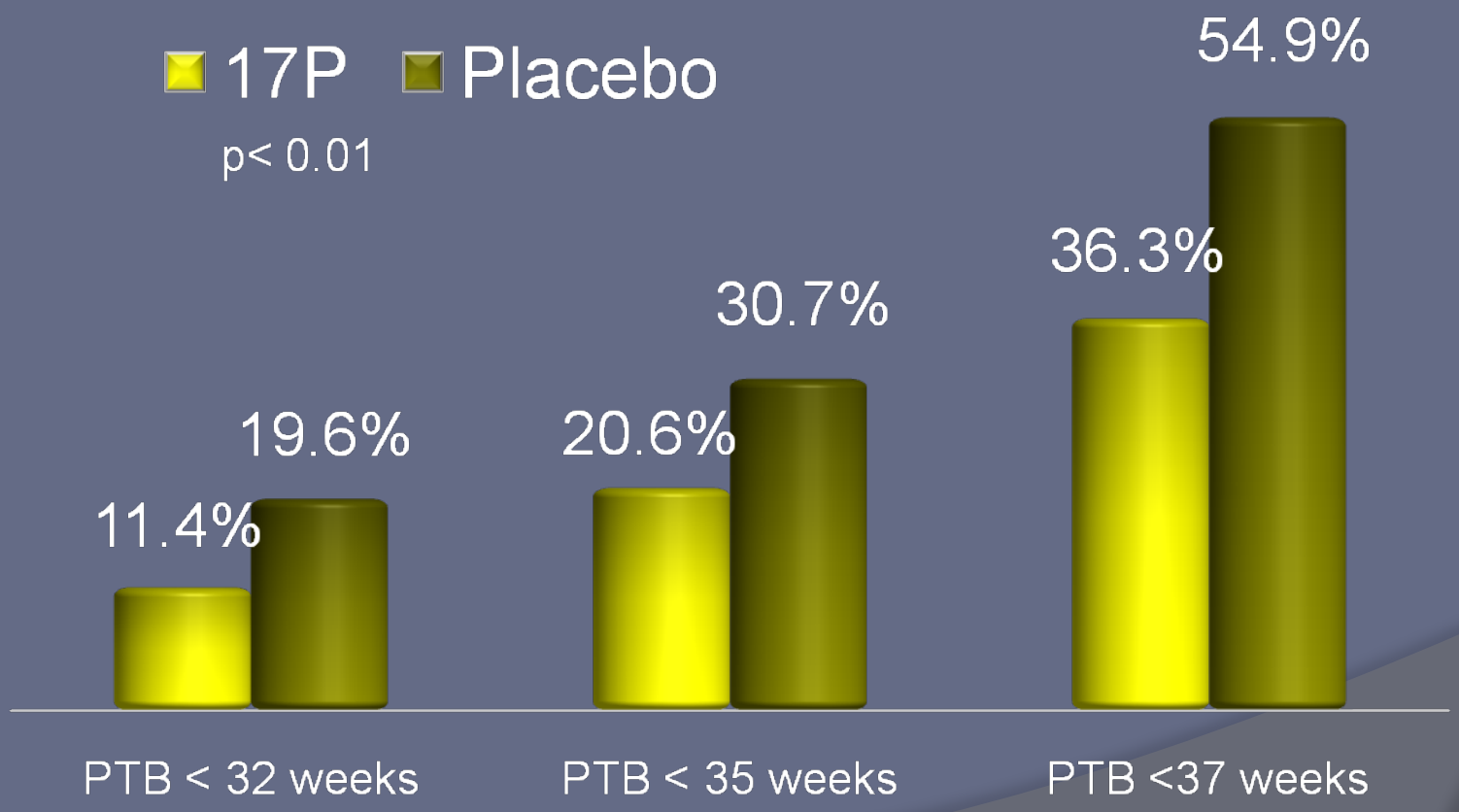
- Study population

	17 P	Placebo
GA prior PTB	30.6 wk	31.3 wk
# prior PTB	1.4	1.6 *
Married	51.3%	46.4%
BMI	26.9	26.0
> 1 prior PTB	27.7%	41.2%
Non-Hispanic Black	59.0%	58.8%
GA at randomization	18.4 wk	18.4 wk

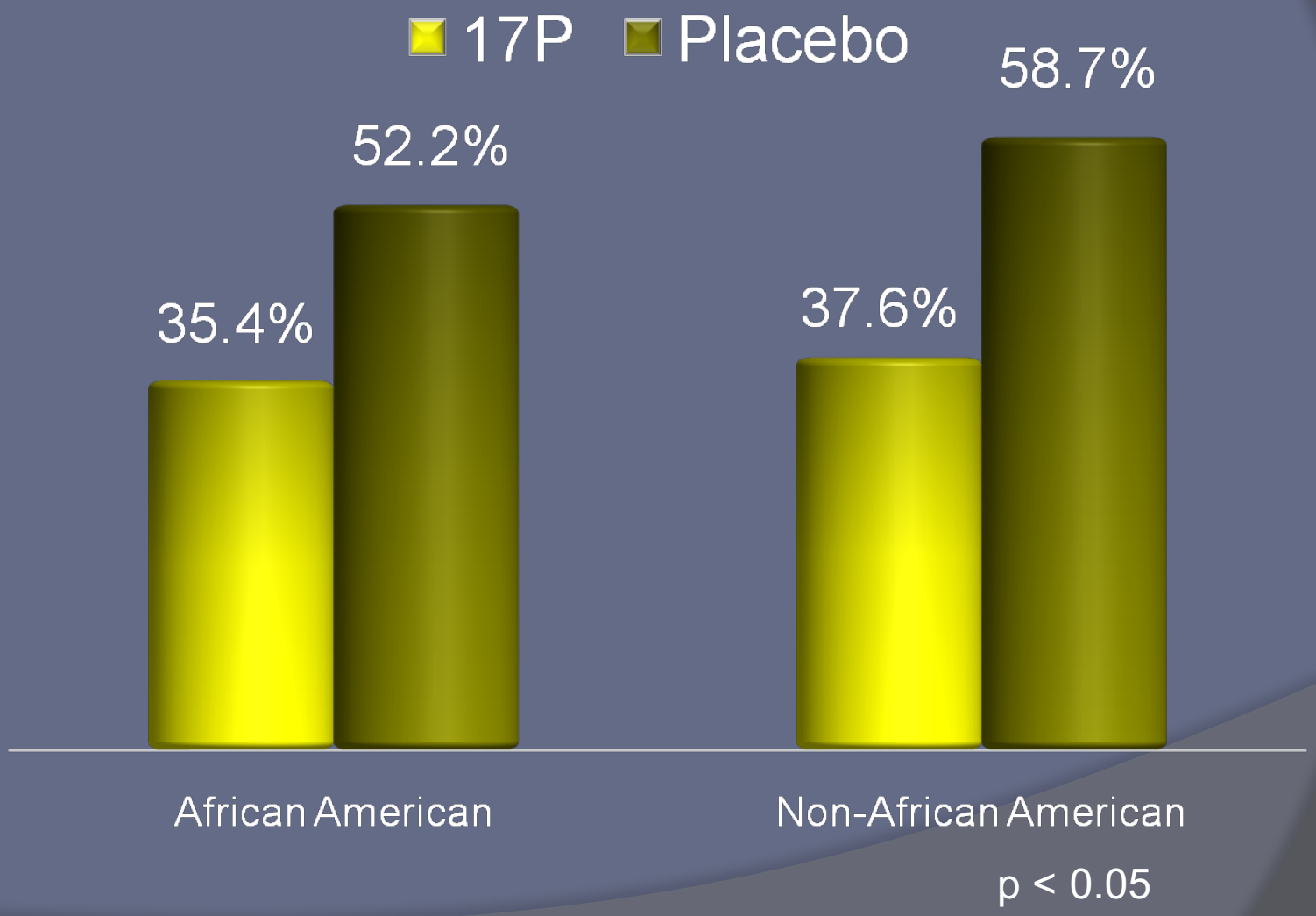
* $p<0.007$

17P – NICHD (Meis, 2003, NEJM)

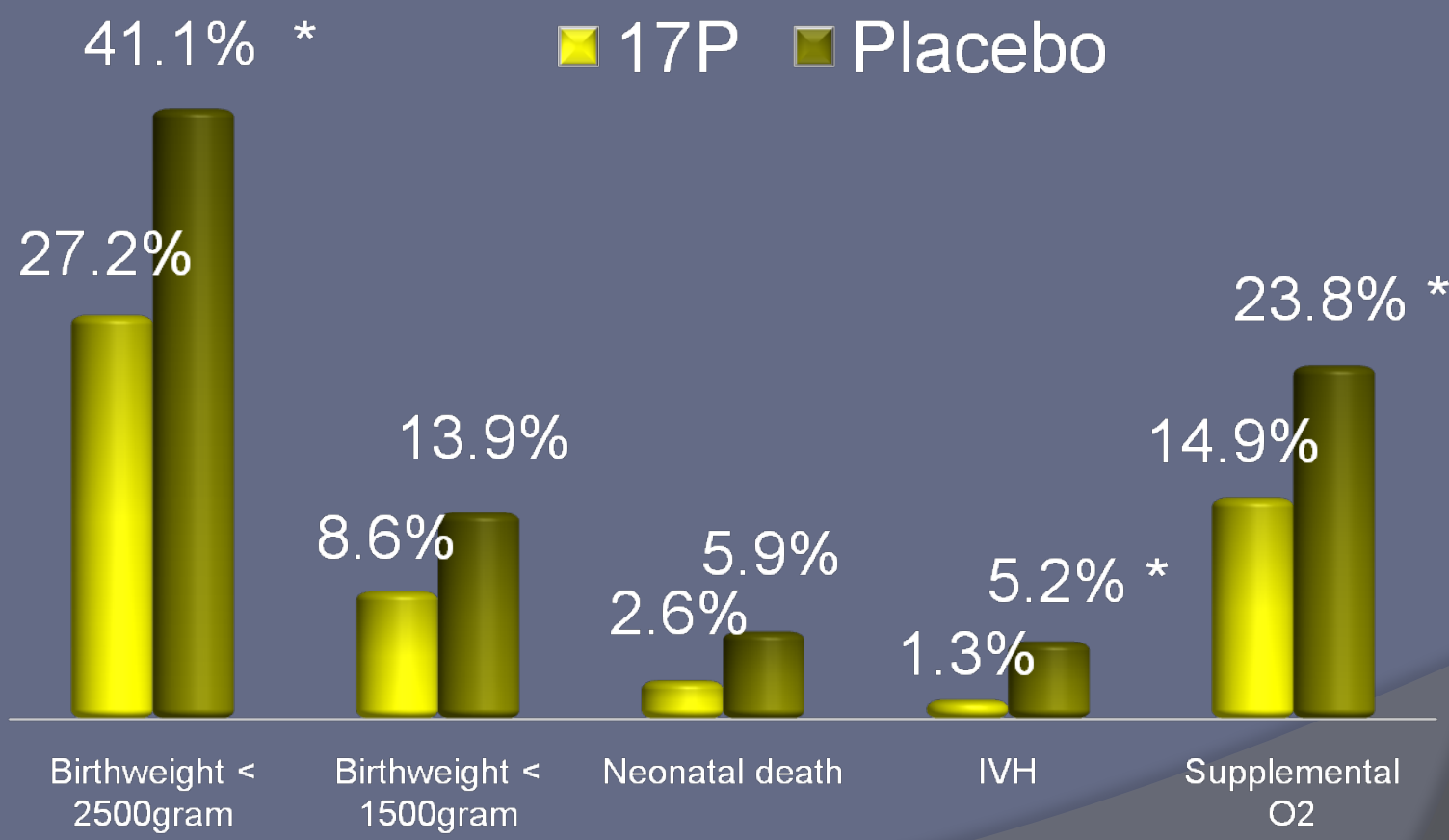
PTB rates



17P – NICHD (Meis, 2003, NEJM)
PTB rates



17P – NICHD (Meis, 2003, NEJM)
Neonatal morbidity



* $p < 0.05$

17P – NICHD (Meis, 2003, NEJM)

- Summary
- Weekly 17P
  - 34% reduction in PTB < 37 weeks
  - 33% reduction in PTB < 35 weeks
  - 42% reduction in PTB < 32 weeks
- Number need to treat
  - 5-6 (95% CI 3.6, 11) for prevention of 1 PTB < 37
  - 12 (95% CI 6.3, 74.6) for PTB < 32

17 – P: Safety

- Rebarber, 2007, Diabetes Care
  - 17-P associated with 3 x increased risk of GDM (95% CI 2.1,4.1)
    - 12.9% vs. 4.9%
- 4 year outcome of exposed children
  - No congenital anomalies
  - Normal neurological development

Northern AT, Norman GS, Anderson K, et al. Obstet Gynecol 2007;110:865–872.

17 –P side effects

- Meis, 2003 NEJM – injection site s/s

Symptom	%
Soreness	34.2
Swelling	14.1
Itching	11.3
Bruising	6.7

Cost effective

- Obido, et al (2006) Obstetrics and Gynecology
  - Modeled 17P costs vs. costs of PTB
- 17P cost effective
  - Prevention of PTB
    - Prior preterm birth <32 weeks
    - Prior preterm birth 32-37 weeks

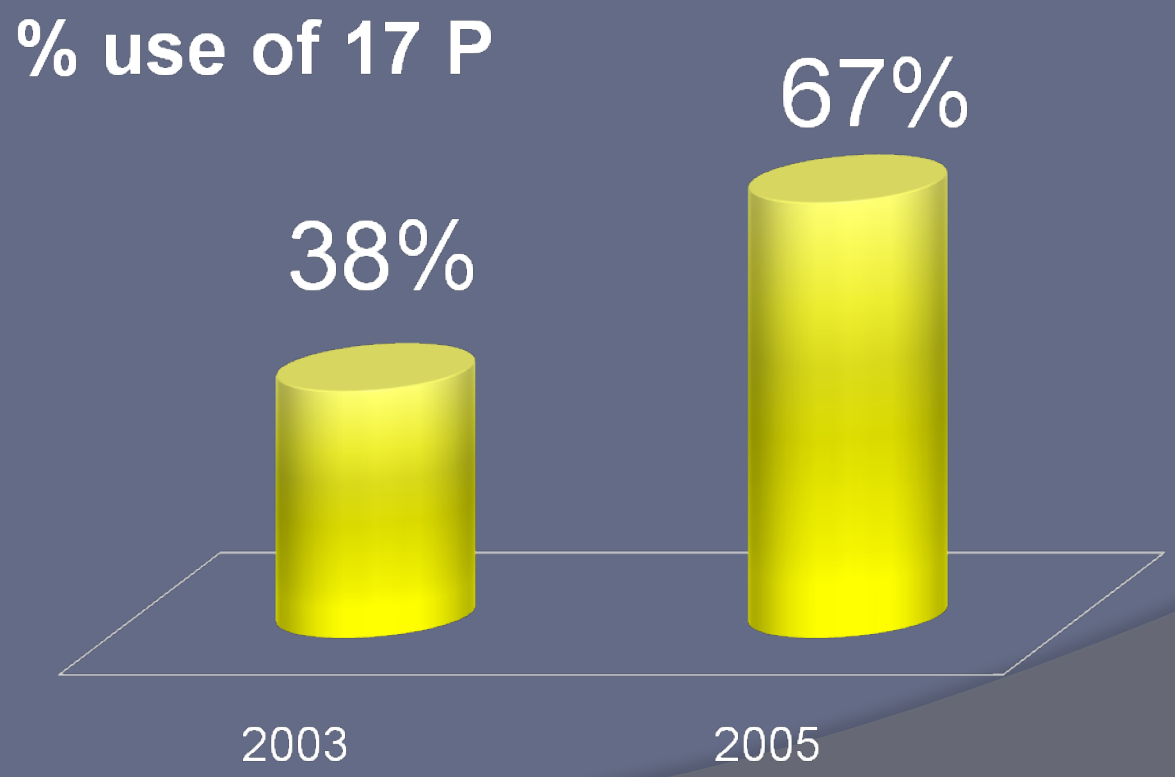
17 P costs/savings

- Modeled costs of 17 P and PTB
- Use of 17 P with prior SPTB
  - Savings
    - $3800 per woman treated
    - $15,900 per infant treated
  - Total - $2 billion annual savings

Bailit JL, Votruba ME.. Am J Obstet Gynecol

Use of 17 P among MFM physicians

- Ness, 2006 AJOG, survey



17 – P twins and triplets

- High risk populations
- NICHD trials of 17P vs. placebo
- Twins – no difference in PTB
  - No difference in morbidity
- Triplets – no difference in PTB

Rouse, NEJM, 2007
Caritis, Obstet Gynecol 2009

Other progesterone trials

- O'Brien, Ultrasound Ob/Gyn, 2007
  - Vaginal progesterone gel, similar population
  - 90 mg progesterone (Crinone®)
  - No difference in PTB < 32 weeks

- deFonseca, Am J Obstet Gyneol, 2003
  - 100mg micronized vaginal progesterone
  - reduction in PTB <34 weeks in progesterone group (2.7% vs. 18.6%)

Other progesterone trials

- Fonseca, NEJM, 2007
  - Cervical length at 22 weeks <15mm
  - 200mg micronized vaginal progesterone
  - 44% reduction in PTB <34 weeks in progesterone group (19% vs. 34.4%)

ACOG/SMFM Recommendations

How to give it

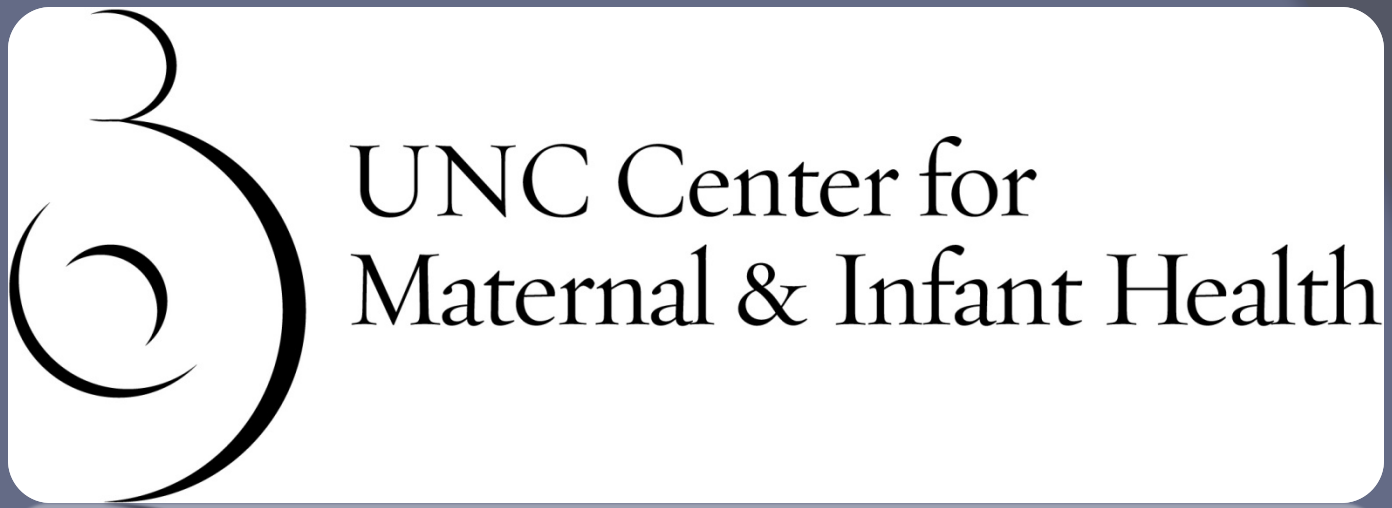
- **17 alpha OHP – 250 mg IM weekly**
- **Start 16-20 weeks EGA**
- **Continue to completed 36th week**
- **Ok to use in diabetes**

Obstetrics and Gynecology, Vol 112(4), 2008

ACOG/SMFM Recommendations

- Not recommended
  - Tocolytic
  - Supplement to cerclage
  - + FFN in asymptomatic patient
  - Therapeutic agent after tocolysis
  - Multiple gestations

Obstetrics and Gynecology, Vol 112(4), 2008



Questions or to discuss if a patient is a 17 P candidate:
william_goodnight@med.unc.edu