17 α-Hydroxyprogesterone Caproate Injection, 250 mg/mL NDA 21-945

Adeza Biomedical

Advisory Committee Meeting

Reproductive Health Drugs

August 29, 2006

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Vice President, Medical Affairs

Adeza Biomedical

Presentation

- Adeza Biomedical
- Medical Need
- Clinical Review
  - Efficacy
  - Safety
- Benefit / Risk

Presenters

Durlin E Hickok, MD, MPH
Vice President, Medical Affairs
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Professor, Obstetrics and Gynecology
University of California, Irvine

External Experts

Paul J Meis, MD	Professor of Obstetrics and Gynecology Wake Forest University
Gwendolyn Norman, RN, MPH	Perinatal Research Nurse Coordinator Wayne State University
Michael O'Shea, MD, MPH	Professor of Pediatrics Wake Forest University
Melissa Parisi, MD, PhD	Assistant Professor of Pediatrics University of Washington
David A Savitz, PhD	Professor of Community and Preventive Medicine Mount Sinai School of Medicine
Frank Stanczyk, PhD	Professor of Obstetrics and Gynecology University of Southern California

Adeza Biomedical

- Medical technology company
- Focused on pregnancy-related and female reproductive disorders
  - preterm birth
  - infertility
- Submitted NDA for FDA approval to market 17P in the US for the prevention of recurrent preterm birth

Nomenclature

17-HPC

- 17 α-hydroxyprogesterone caproate

17P

- Clinical study formulation of 17-HPC for injection used in the NICHD Study

Gestiva™

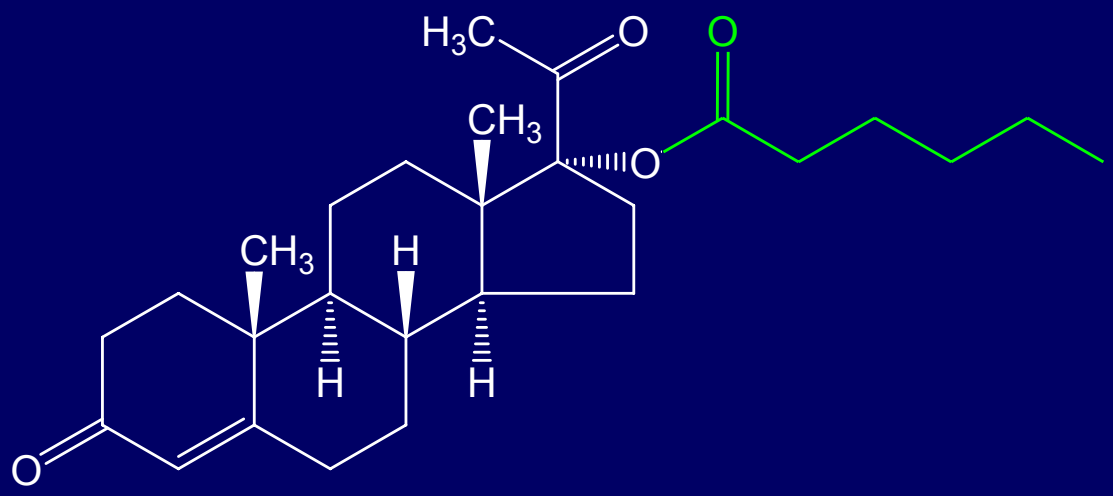
- Adeza's proposed trade name for 17P

Delalutin®

- Trade name of previously marketed 17-HPC

17-HPC

- 17 α-hydroxyprogesterone caproate
  - The active pharmaceutical ingredient of 17P
  - An esterified derivative of the naturally occurring 17 α-hydroxyprogesterone
  - Substantial progestational activity
  - Prolonged duration of action



17P

- 17P is a sterile solution for injection containing:
  - 17-HPC (250 mg/mL)
  - Castor oil USP
  - Benzyl benzoate USP
  - Benzyl alcohol NF
- 17P
  - Used in NICHD clinical studies
  - Identical in composition to previously marketed Delalutin

17-HPC – History

- Delalutin approved by FDA in 1956
  - Indications
    - treatment of habitual and recurrent miscarriage
    - threatened miscarriage
    - postpartum after pains
    - advanced uterine cancer
  - Voluntarily withdrawn from US market in 1999 for reasons not related to safety or effectiveness
- Multiple studies evaluated safety and efficacy of 17-HPC for prevention of preterm birth

17-HPC Studies for Preterm Birth

	Inclusion Factors	Initiated	Ended	Dose (mg/wk)	Odds Ratio
LeVine (1964)	3 miscarriages	<16 wks	36 wks	500	0.63 (0.10-4.15)[a]
Papiernik (1970)	High Preterm Risk Score	28-32 wks	≤8 doses	250 mg q 3days	0.24 (0.07-0.82)[a]
Johnson (1975)	2 miscarriages or 2 preterm births	First visit	37 wks	250	0.12 (0.02-0.85)[a]

[a]Odds ratios reported by Keirse 1989

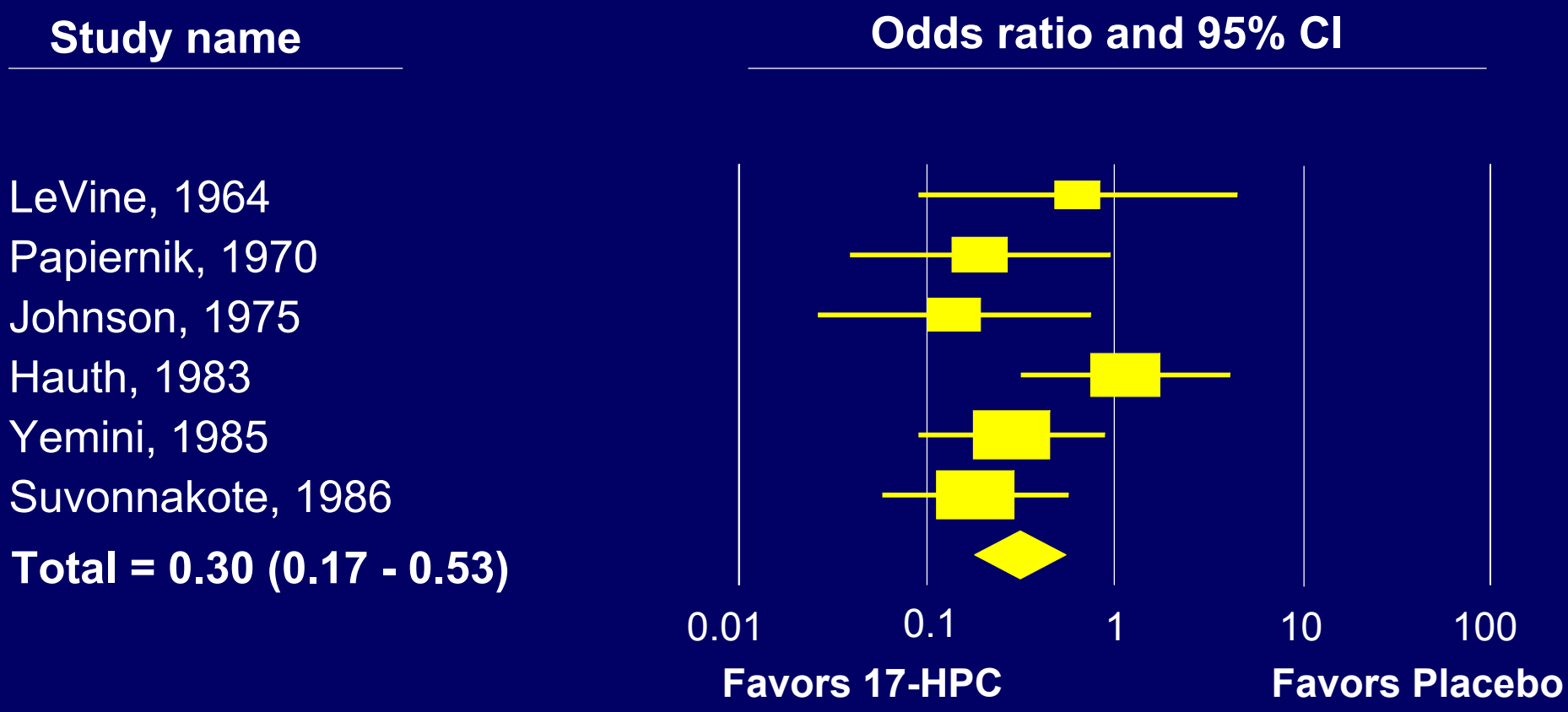
17-HPC Studies for Preterm Birth (continued)

	Inclusion Factors	Initiated	Ended	Dose (mg/wk)	Odds Ratio
Hauth (1983)	Active duty military	16-20 wks	36 wks	1000	1.11 (0.31-3.97)
Yemeni (1985)	2 preterm births or 2 miscarriages	First visit (mean GA 12.2 wks)	37 wks	250	0.30 (0.11-0.84)[a]
Suvonnakote (1986)	1 preterm birth or 2 midtrimester miscarriages	16-20 wks	37 wks	250	0.29 (0.12-0.70)

[a]Odds ratios reported by Keirse 1989

17-HPC Studies for Preterm Birth – Forest Plot

Treatment Effect of 17-HPC



Meta Analysis

Development of 17P NDA Submission

- NICHD conducted controlled clinical study evaluating 17P for prevention of recurrent preterm birth
- Results published in *New England Journal of Medicine*, 2003
- Adeza allowed access to clinical database

Development of 17P NDA Submission

- Results from NICHD study provide primary basis for efficacy claim of Adeza's NDA submission for 17P
  - Large, multicenter study
  - Highly statistically significant efficacy findings
  - Study stopped early by DSMC for efficacy
  - Results consistent across subsets of patients

Proposed Indication for Gestiva (17P)

"Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth."

Medical Need

Michael P Nageotte, MD

Professor, Obstetrics & Gynecology

University of California, Irvine

Immediate Past President

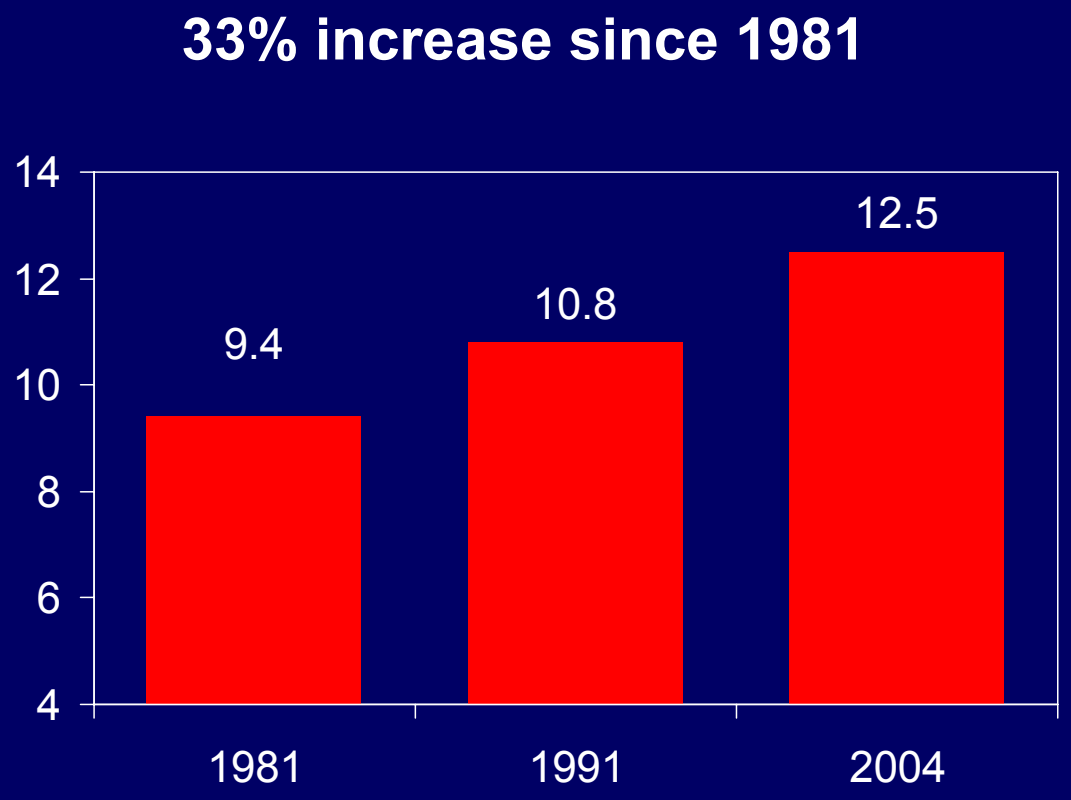
Society for Maternal-Fetal Medicine

Definition of Preterm Birth

- Preterm birth is defined as birth before the 37th week of gestation

Preterm Birth in the US

- Incidence of preterm birth continues to rise[a]
- Costs exceed $26 billion annually
- One preterm birth occurs every minute in the US
- March of Dimes launched a multimillion dollar campaign to reduce preterm births
- Reduction in preterm births will alleviate primary cause of perinatal and neonatal morbidity and mortality[b]



[a]Hamilton BE et al. *Natl Vital Stat Rep*. 54(8):1-17; 2005

[b]Spong CY. *Obstet Gynecol*. 101(6):1153-4; 2003

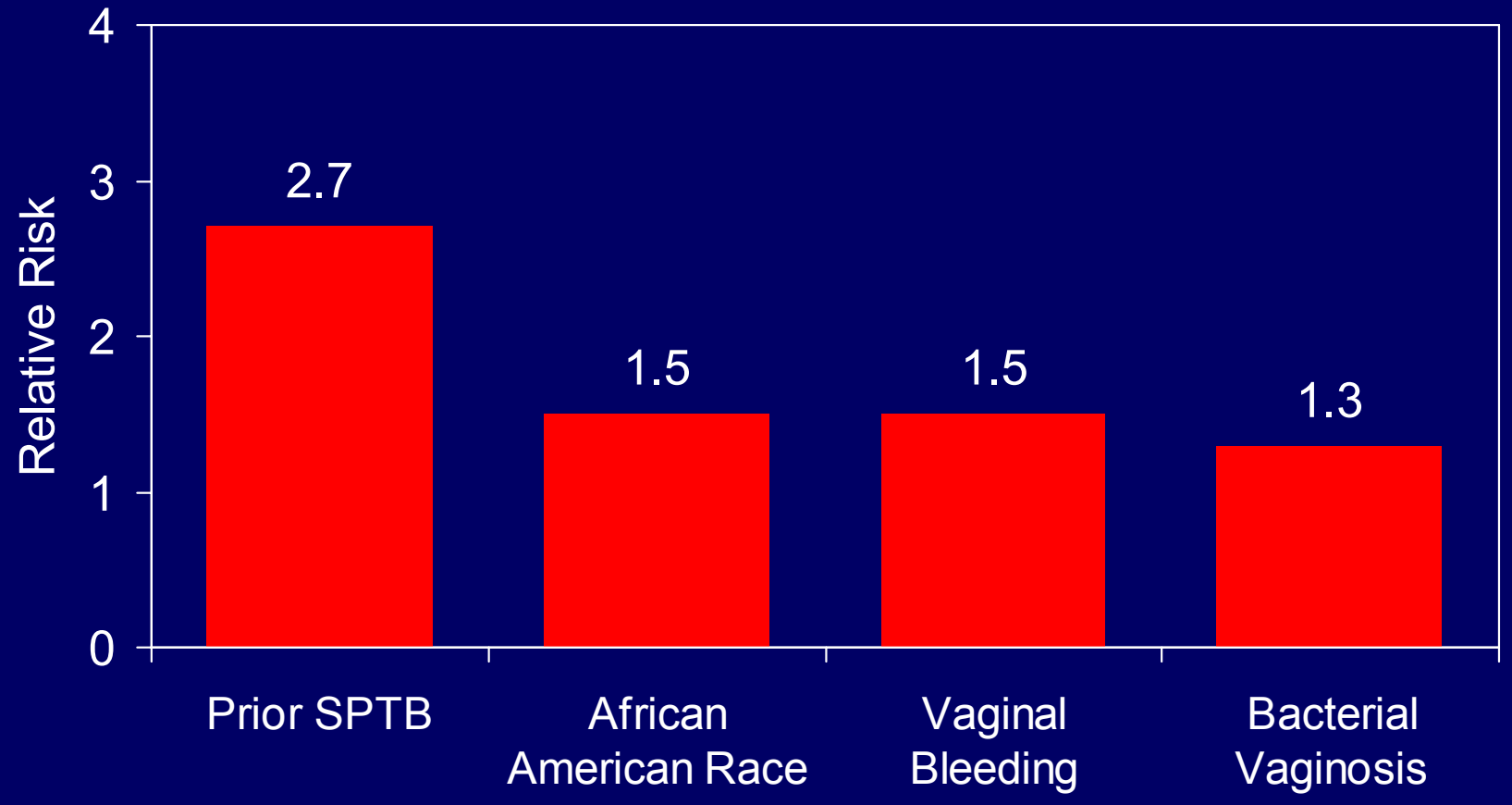
Morbidities Associated with Preterm Birth

- Respiratory distress syndrome (RDS)
- Intraventricular hemorrhage (IVH)
- Periventricular leukomalacia (PVL)
- Necrotizing enterocolitis (NEC)
- Apnea
- Jaundice
- Anemia
- Infections due to immature immune systems
- Neonatal death

Neonatal Long-Term Morbidities

- Potential long-term outcomes
  - Retinopathy
  - Cerebral palsy
  - Mental retardation
  - Learning disabilities
  - Attention deficit disorders

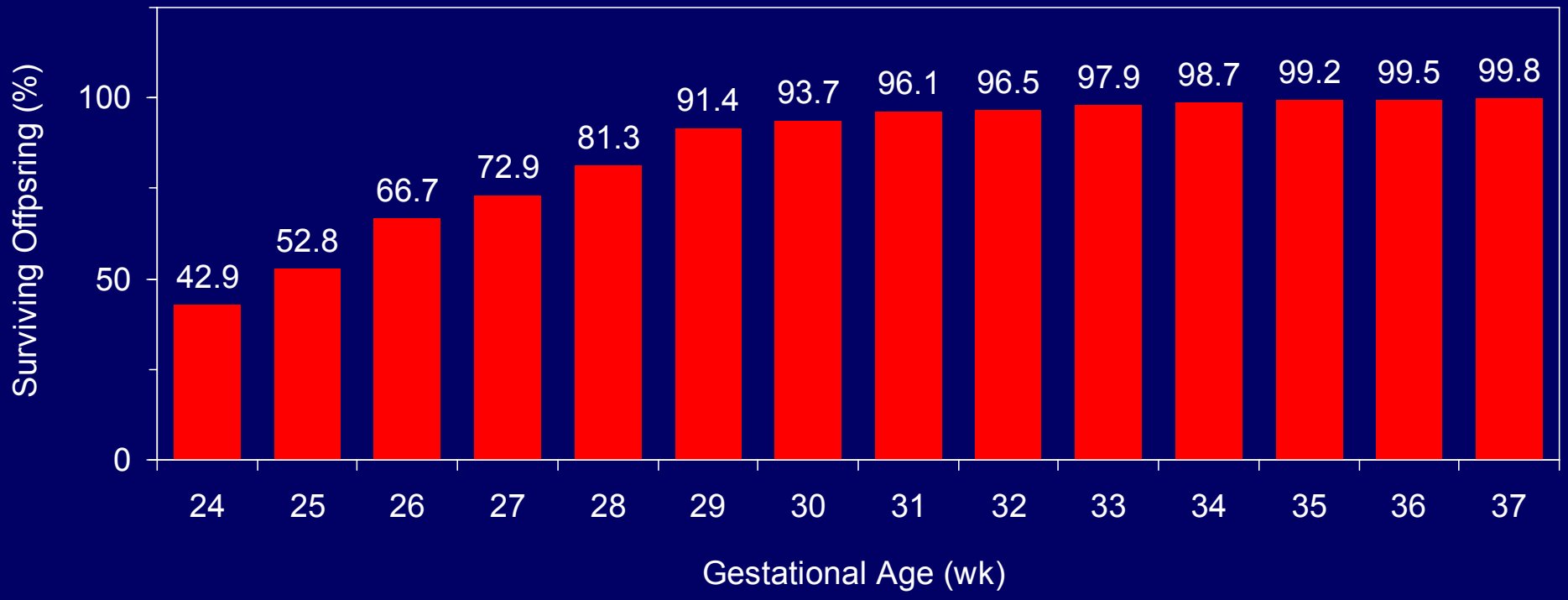
Risk Factors for Preterm Birth



From: Goldenberg RL et al. *Am J Public Health.* 88:233-238; 1998

Benefits of Prolonging Pregnancy – Mortality

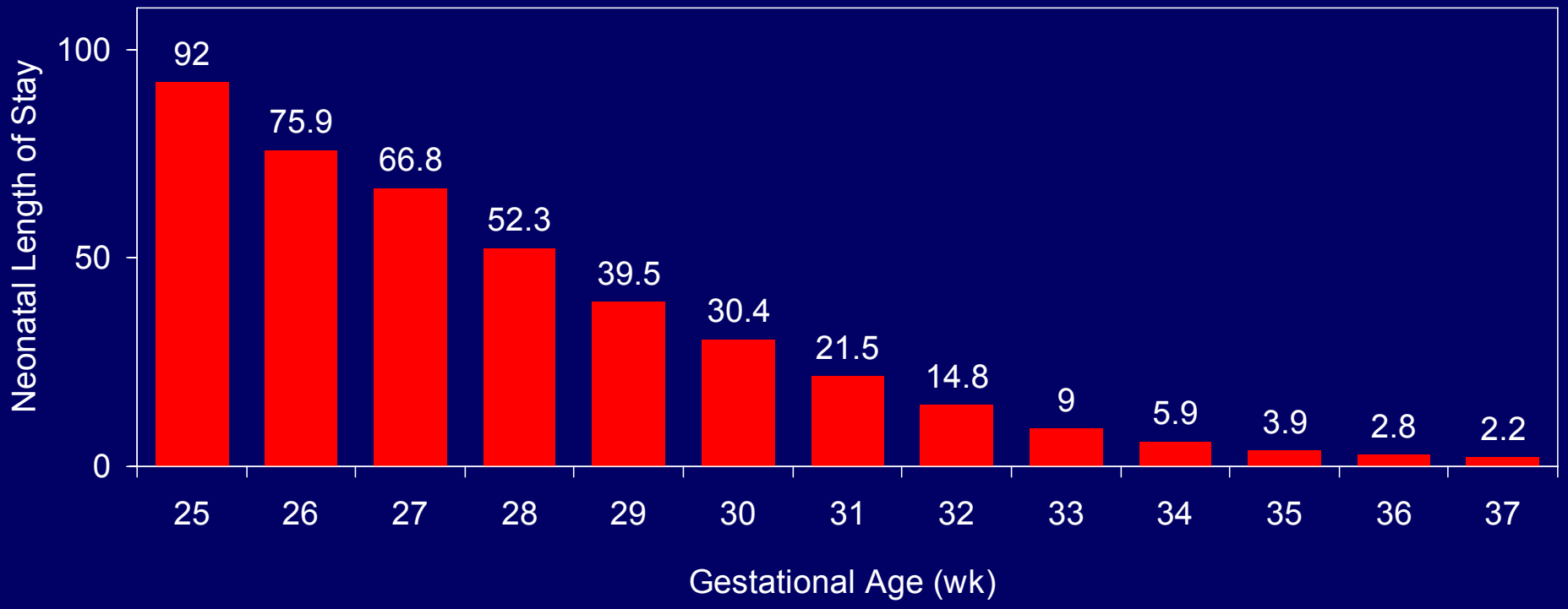
- Improved survival with gestational age



From: St. John EB et al. *J Obstet Gynecol.* 182:170-175; 2000

Benefits of Prolonging Pregnancy – Length of Stay

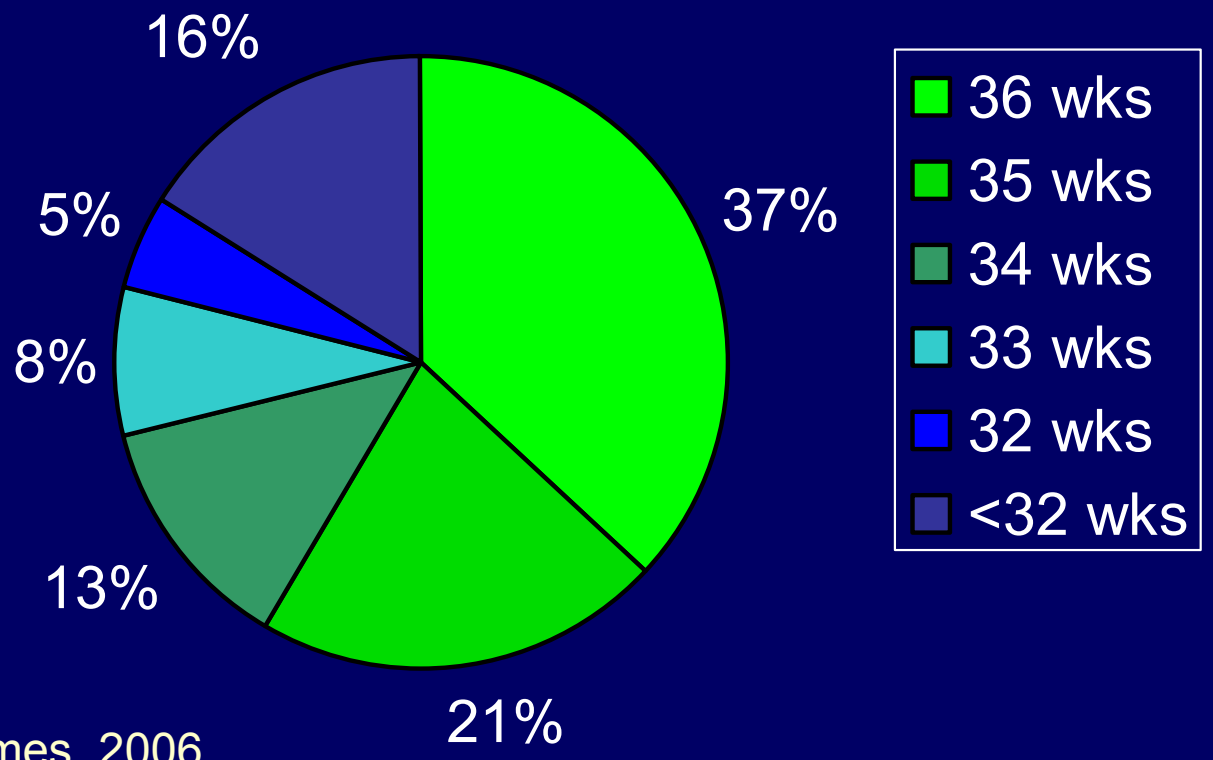
- Reduced neonatal hospital days



From: Gilbert WM et al. *Obstet Gynecol.* 102:488-492; 2003

Significance of Late Preterm Birth

- Contributes substantially to overall preterm births
  - 58% between 35-36 weeks
  - 79% greater than 32 weeks



From: March of Dimes, 2006

Significance of Late Preterm Birth

- Increased mortality[a]
  - Mortality risk approximately 3-fold higher at 35-36 weeks
- Increased morbidities[b,c]
  - Respiratory distress requiring O_2
  - Temperature instability
  - Hypoglycemia
  - Jaundice
  - Attention deficit disorders
- Increased hospitalizations and associated costs[b,c]
  - Initial hospitalization costs approximately 3-fold higher
  - Risk for rehospitalization from 2 weeks to 6 months post discharge increased

[a]Kramer MS et al. *JAMA*. 284:843-9; 2000
[b]Wang ML et al. *Pediatrics*. 114:372-6; 2004
[c]Escobar GJ et al. *Semin Perinatol*. 30(1):28-33; 2006

Available Treatments

- Treatment of preterm labor
  - Tocolytics effective for short-term prolongation after onset of labor
- Prevention of preterm birth
  - No effective treatments identified prior to 17P
  - American College of Obstetricians and Gynecologists (ACOG) recommends use to prevent recurrent preterm birth in 2003 after publication of the NICHD study[a,b]
  - 17P currently in use among Ob/Gyn community for prevention of recurrent preterm birth

[a]ACOG News Release, 2003
[b]ACOG Committee Opinion. *Obstet Gynecol*. 102(5 pt 1):1115-6; 2003

Current Availability of 17P

- Available only from compounding pharmacies
  - No consistent labeling/prescribing information
  - Limited FDA oversight
  - No regulations ensuring consistency of products between compounding pharmacies
  - No federal regulations requiring reporting of AE/SAEs (MedWatch)

Conclusions

- Compelling need to address rising incidence of preterm birth and associated costs and morbidities
- Benefits of prolonging pregnancy at any gestation
  - Prevention of early preterm births
  - Prevention of late preterm births
- Need for FDA-approved product

Clinical Review

National Institute of Child Health and Human Development (NICHD)

- Part of the National Institutes of Health (NIH)
- Objectives
  - Identify causes of prematurity
  - Evaluate safety and effectiveness of treatments
- Maternal-Fetal Medicine Units (MFMU) Network
  - Consists of major medical training institutions
  - Engages in multicenter collaborative investigations

NICHD MFMU Network Sites for 17P Study

- University of Pittsburgh
- University of Tennessee
- University of Alabama
- Wayne State University
- University of Cincinnati
- Wake Forest University
- University of Chicago
- Ohio State University
- University of Miami
- University of Texas Southwestern
- University of Texas San Antonio
- University of Utah
- Thomas Jefferson University
- Brown University
- Columbia University
- Case Western University
- University of Texas Houston
- University of North Carolina
- Northwestern University

Overview of NICHD Clinical Studies

- Study 002
  - Initiated in 1999, completed in 2002
  - Randomized, placebo-controlled, double-blind, multi-center clinical study
  - Weekly IM injections from 16^0 and 20^6 weeks of gestation until 36^6 weeks gestation or birth
  - Enrolled 463 patients in 2:1 ratio active to placebo
  - DSMC recommended study be halted early
    - Interim analysis conducted on 351 completed patients
    - Boundary for test of significance had been crossed
    - Indicated a benefit for 17P in reducing preterm birth
  - Results form primary basis for efficacy

Overview of NICHD Clinical Studies

- Study 001
  - Initiated in 1998
  - Terminated due to manufacturer and FDA recall of study drug
  - Enrolled only 150 of 500 planned patients

Overview of NICHD Clinical Studies

- Follow-Up Study
  - Observational follow-up safety study to assess the long term safety outcome of infants exposed to 17P in utero
  - Examined health and development of infants born during Study 002
  - Conducted at 15 MFMU Network study centers
  - Enrolled 278 children

Efficacy and Safety Databases

Efficacy Assessment

- Study 002

Safety Assessment

- Study 002
- Study 001
- Follow-Up Study

Efficacy

Enrollment Criteria

- Pregnant women with documented history of previous singleton spontaneous preterm delivery (SPTD)
- Gestational age of 16^0 to 20^6 weeks at randomization
- Exclusion criteria:
  - Multifetal gestation
  - Known major fetal anomaly or fetal demise
  - Prior progesterone treatment during current pregnancy
  - Prior heparin therapy during current pregnancy
  - History of thromboembolic disease
  - History of maternal medical/obstetrical complications (eg current or planned cerclage, HTN requiring medications, seizure disorder)

Patient Enrollment – Study 002

- Total of 463 patients
  - 2:1 randomization (active:placebo)
  - 310 in 17P group
  - 153 in Placebo group
- 418 (90.3%) patients completed injections through 36^6 weeks gestation or birth
  - 279 (90.0%) in 17P group
  - 139 (90.8%) in Placebo group

Baseline Demographics

Characteristic	17P (N=310)	Placebo (N=153)	P value
Age, yr mean (SD)	26.0 (5.6)	26.5 (5.4)	0.2481
Race or ethnic group			0.8736
African American	59.0%	58.8%	
Caucasian	25.5%	22.2%	
Hispanic	13.9%	17.0%	
Asian	0.6%	0.7%	
Other	1.0%	1.3%	
Marital status			0.6076
Married or living with partner	51.3%	46.4%	
Divorced, widowed or separated	10.3%	11.8%	
Never married	38.4%	41.8%	
Years of education, mean (SD)	11.7 (2.3)	11.9 (2.3)	0.2175

Baseline Pregnancy Characteristics

Characteristic	17P (N=310)	Placebo (N=153)	P value
Body mass index (kg/m^2), mean (SD)	26.9 (7.9)	26.0 (7.0)	0.3310
Diabetes	4.2%	2.6%	0.3954
Smoked cigarettes during pregnancy	22.6%	19.6%	0.4647
Alcoholic drinks during pregnancy	8.7%	6.5%	0.4172
Used street drugs during pregnancy	3.5%	2.6%	0.7822
Duration of gestation at randomization (wk), mean (SD)	18.9 (1.4)	18.8 (1.5)	0.5929

Previous Obstetrical History

Obstetrical History	17P (N=310)	Placebo (N=153)	P value
Number previous SPTD, mean (SD)	1.3 (0.7)	1.5 (0.9)	0.0017
>1 Previous PTB	27.7%	41.2%	0.0036
Gestational age qualifying delivery (wk), mean (SD)	30.6 (4.6)	31.3 (4.2)	0.2078
Previous miscarriage	30.0%	37.3%	0.1166

Efficacy Endpoints – Primary

- Preterm birth <37 weeks

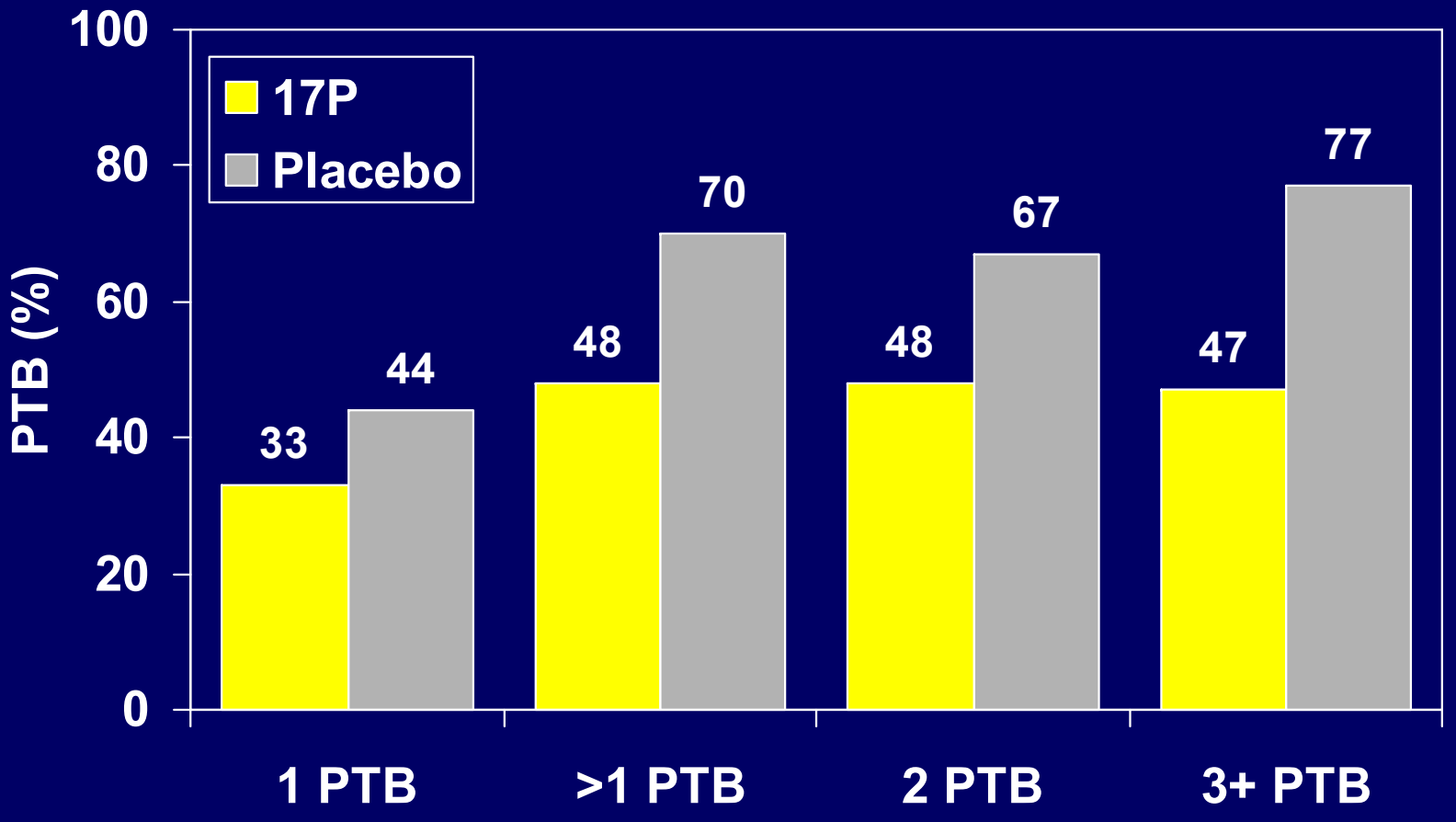
Primary Efficacy Results
Preterm Birth <37 Weeks

Population	17P N (%)	Placebo N (%)	P value
Intent-to-treat	310 (37.1)	153 (54.9)	0.0003
			0.0010[a]
All available data[b]	306 (36.3)	153 (54.9)	0.0001
			0.0006[a]

[a]P value from a logistic regression adjusting for the number of previous preterm deliveries
[b]Analysis population represents that reported by Meis et al (2003) and excludes 4 patients lost to follow-up

Preterm Birth <37 Weeks of Gestation

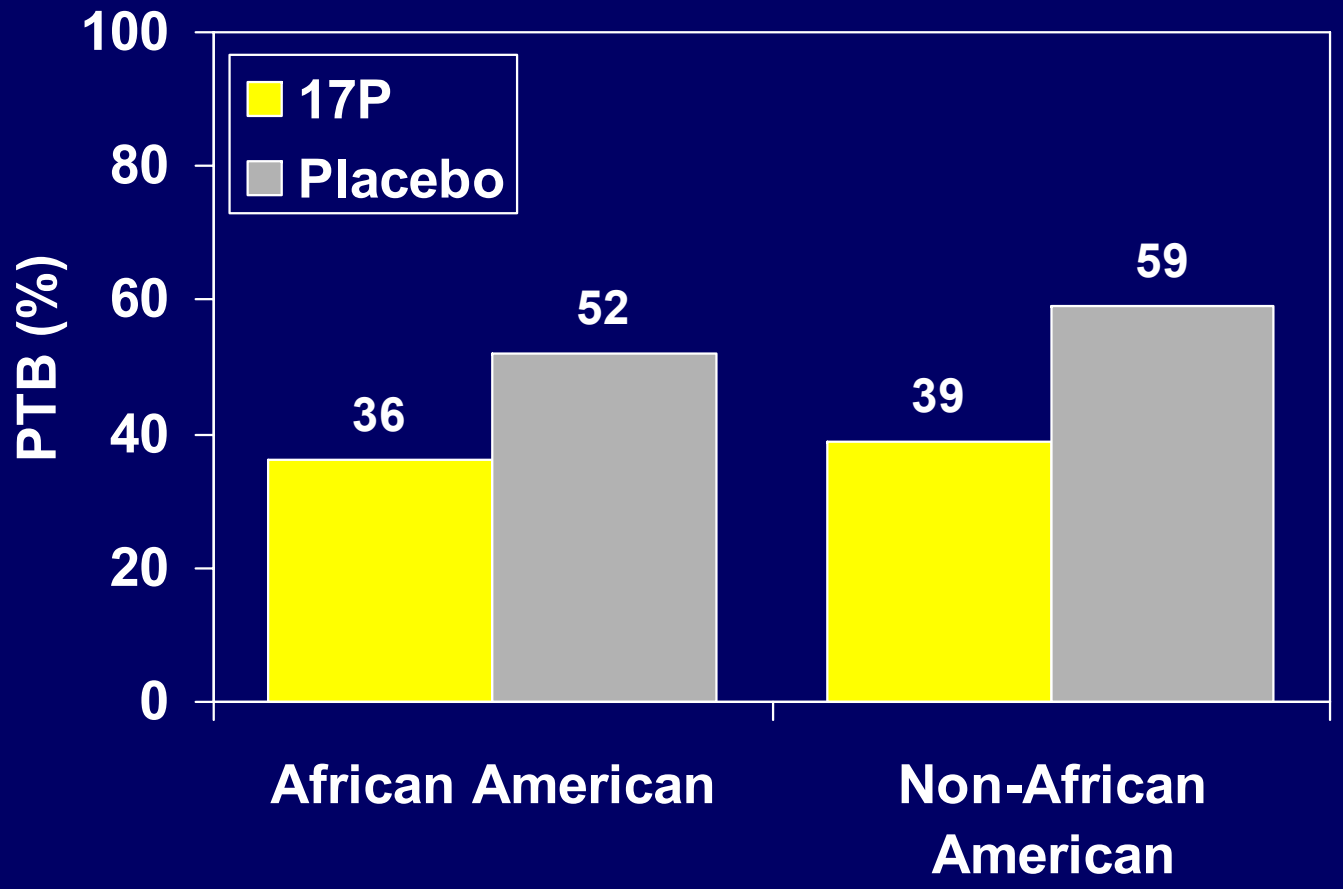
Number of Previous Preterm Births



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

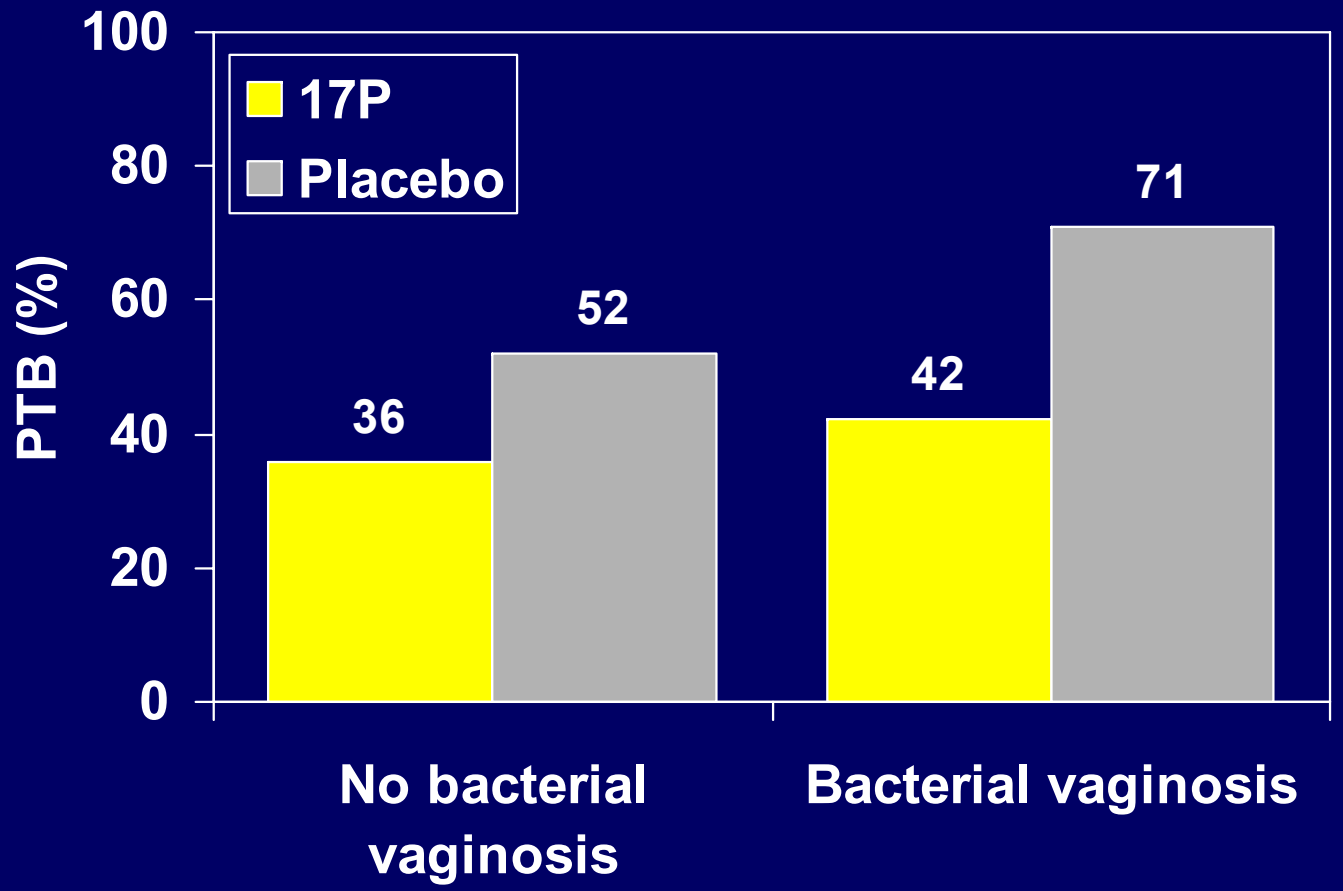
Race



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

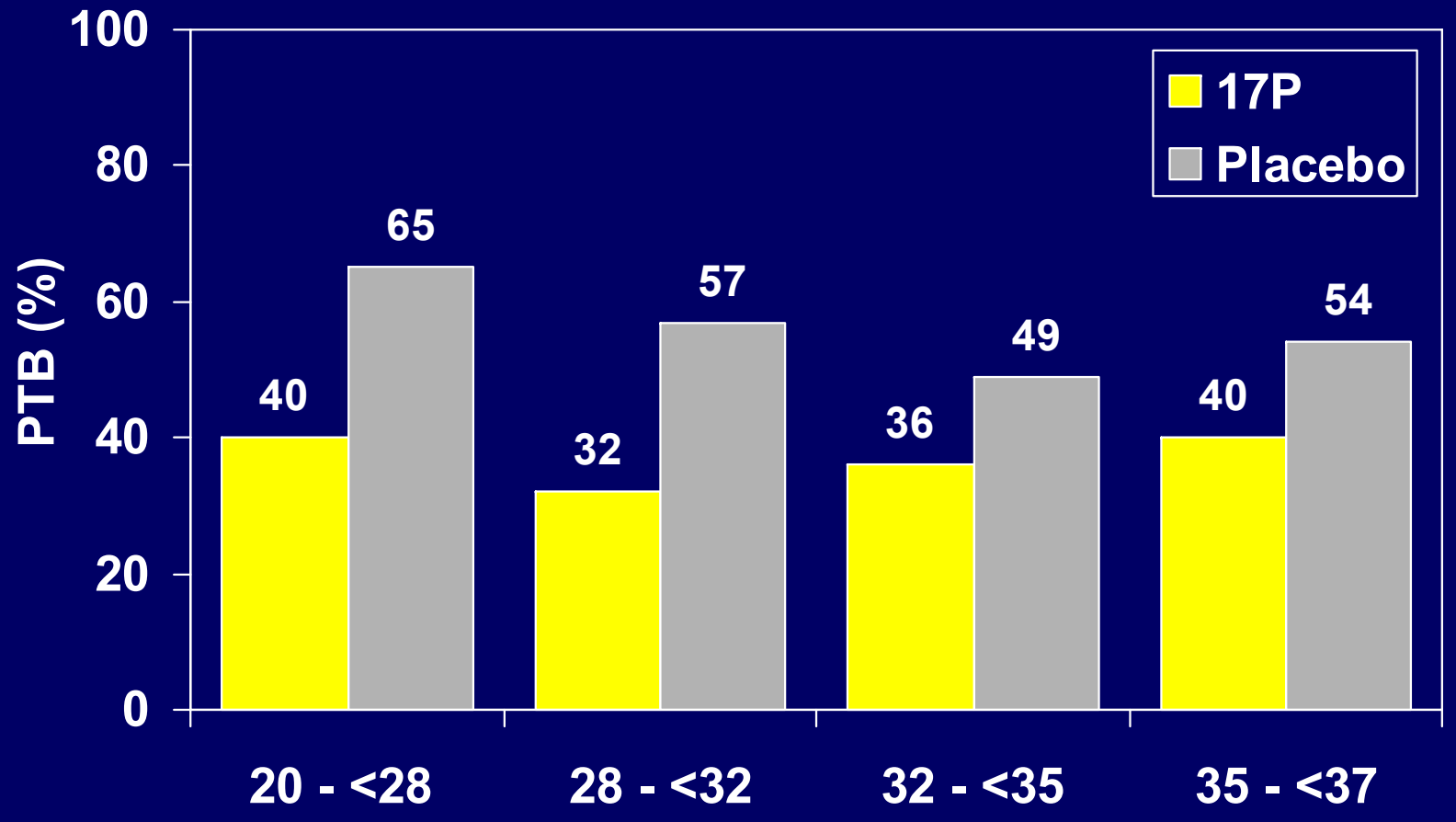
Bacterial Vaginosis



Breslow-Day P value >0.05

Preterm Birth <37 Weeks of Gestation

Gestational Age of Qualifying Preterm Birth



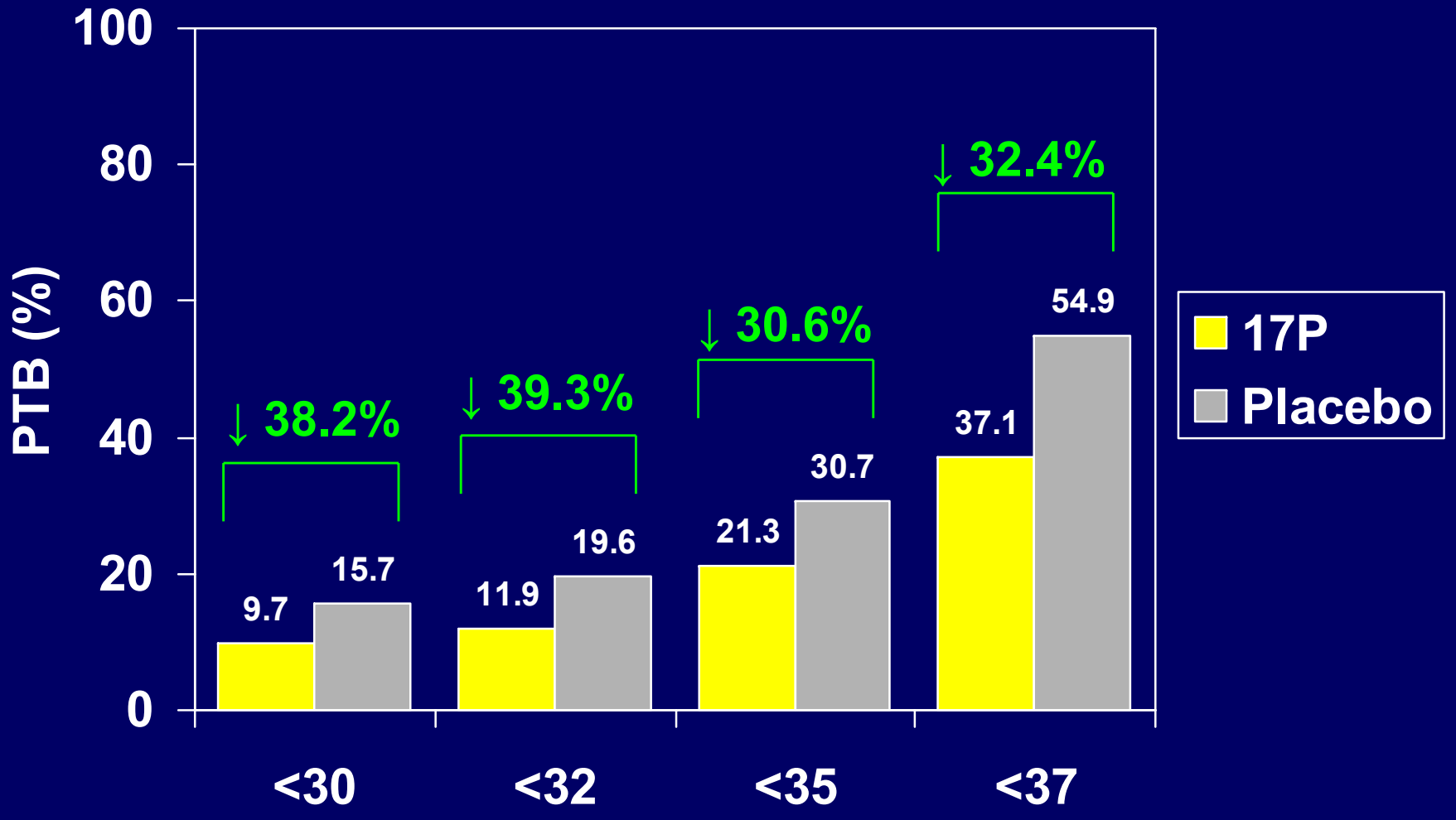
Breslow-Day P value >0.05

Secondary Maternal Efficacy Endpoint Results

Pregnancy Outcome	17P (N=310) %	Placebo (N=153) %	P value
Preterm birth $<35^0$ weeks	21.3	30.7	0.0263
Preterm birth $<32^0$ weeks	11.9	19.6	0.0273
Preterm birth $<30^0$ weeks	9.7	15.7	0.0581

Note: Data from the 4 patients lost to follow-up are included based upon last known date pregnant

Preterm Birth <37, <35, <32, and <30 Weeks



Note: Data from the 4 patients lost to follow-up are included based upon last known date pregnant

Gestational Ages at Birth

Gestational Age at Birth	17P (N=310) %	Placebo (N=153) %
Term (>37 weeks)	62.9	45.1
35^{0}-36^{6} weeks	15.8	24.2
32^{0}-34^{6} weeks	9.4	11.1
28^{0}-31^{6} weeks	2.6	9.2
24^{0}-27^{6} weeks	3.9	7.2
20^{0}-23^{6} weeks	3.6	3.3
16^{0}-19^{6} weeks	1.9	0
Total	100%	100%

Hazard Ratio for Delivery

Gestational Age at Delivery	Hazard Ratio	95% Confidence Interval
Term (>37 weeks)	1.00	–
35^{0}-36^{6} weeks	0.52	0.28 – 0.94
32^{0}-34^{6} weeks	0.73	0.31 – 1.70
28^{0}-31^{6} weeks	0.27	0.08 – 0.90
24^{0}-27^{6} weeks	0.54	0.17 – 1.72
20^{0}-23^{6} weeks	1.01	0.23 – 4.50
16^{0}-19^{6} weeks	NC	NC

NC=not calculable

Neonatal Outcomes

Neonatal Outcome	17P	Placebo	P value
Birthweight			
<2500 g	27.2%	41.1%	0.0029
<1500 g	8.6%	13.9%	0.0834
Birthweight (g), mean (SD)	2760 (859)	2582 (942)	0.0736
Admitted to NICU (live births)	27.8%	36.4%	0.0434
Days in NICU (median)	9.1	14.1	0.1283

Neonatal Morbidities

Neonatal Morbidity	17P	Placebo	P value
Necrotizing enterocolitis (NEC)	**0%**	**2.7%**	**0.0127**
Intraventricular hemorrhage (IVH)	**1.4%**	**5.3%**	**0.0258**
Supplemental oxygen	**15.4%**	**24.2%**	**0.0248**
Days respiratory therapy (mean)	**1.7**	**2.7**	**0.0438**
Ventilator support	8.9%	14.8%	0.0616
Transient tachypnea	3.7%	7.3%	0.0990
Respiratory distress syndrome (RDS)	9.9%	15.3%	0.0900
Bronchopulmonary dysplasia (BPD)	1.4%	3.3%	0.1730
Patent ductus arteriosis (PDA)	2.4%	5.4%	0.1004

Composite Neonatal Morbidity Index

- Conducted as post hoc analysis
- Defined as any liveborn infant who experienced one or more of the following:
  - Death
  - Respiratory distress syndrome (RDS)
  - Bronchopulmonary dysplasia (BPD)
  - Grade 3 or 4 intraventricular hemorrhage (IVH)
  - Proven sepsis
  - Necrotizing enterocolitis (NEC)
- Trend toward improvement with 17P
  - 11.9% in 17P group
  - 17.2% in Placebo group

Summary of NICHD Efficacy Results

Weekly administration of 17P

- Reduces rate of recurrent preterm birth at <37, <35, and <32 weeks
  - prolongs gestation
  - consistent with previous studies
- Improves neonatal outcomes
  - reduced percentage of infants born <2500 g
  - reduced admission rate to NICU
- Reduces specific neonatal morbidities
  - NEC, IVH, supplemental oxygen, mean days of respiratory therapy

Safety

Safety Database

- Study 002
- Study 001
- Follow-Up Study

Safety Database Exposure – Studies 002 and 001

- 613 Patients exposed to at least 1 injection
  - 17P 404 patients
  - Placebo 209 patients

Pregnancy Related Admissions/Procedures

	17P (N=399) %	Placebo (N=205) %	P value
Hospital or labor admission for preterm labor	14.8	15.6	0.7834
Cerclage placement	1.3	1.5	1.0000

Pregnancy Related Complications

Complication	17P (N=399) %	Placebo (N=205) %	P value
Preeclampsia or gestational hypertension	8.3	4.4	0.0795
Gestational diabetes	6.3	3.4	0.1792
Oligohydramnios	3.3	1.5	0.2851
Abruption	1.8	2.9	0.3565
Significant antepartum bleeding	2.5	3.4	0.5654
Clinical chorioamnionitis	3.3	2.4	0.8011
Other complication	2.6	3.0	0.7928

Most Frequently Reported Maternal Adverse Events

	17P (N=404) %	Placebo (N=209) %
Any adverse event (AE)	59.2	56.5
Preferred Term		
Injection site reactions	44.6	40.7
Urticaria	12.6	11.5
Pruritus	6.9	5.3
Contusion	6.4	9.6
Nausea	5.0	3.8

Note: Table presents those adverse events reported by at least 2% of patients in either treatment group

Discontinuations Due to Adverse Events

- Patients discontinued early due to AEs
  - 17P group – 2.2% patients
  - Placebo group – 3.3% patients

- Injection site reactions most common
  - 17P group – 1.0% patients
  - Placebo group – 1.4% patients

Serious Adverse Events

- SAEs collected according to NICHD standardized procedures
  - All deaths (maternal, neonatal, fetal)
  - Other serious and unexpected AEs
- Analysis also included congenital anomalies

Serious Adverse Events – Nonfatal

	17P (N=404) %	Placebo (N=209) %
Any SAEs (Total)	9.4	10.5
Nonfatal SAEs		
Congenital anomalies	2.2	1.9
Injection site reactions	1.0	1.0
Hypersensitivity/adverse drug reaction	0.2	0.5
Infection	0.5	0
Pulmonary embolism (maternal)	0.2	0
Uterine rupture	0.2	0
Pruritus	0	0.5
Arthralgia	0.2	0
Testicular infarction	0.2	0

Congenital Anomalies Assessed at Birth

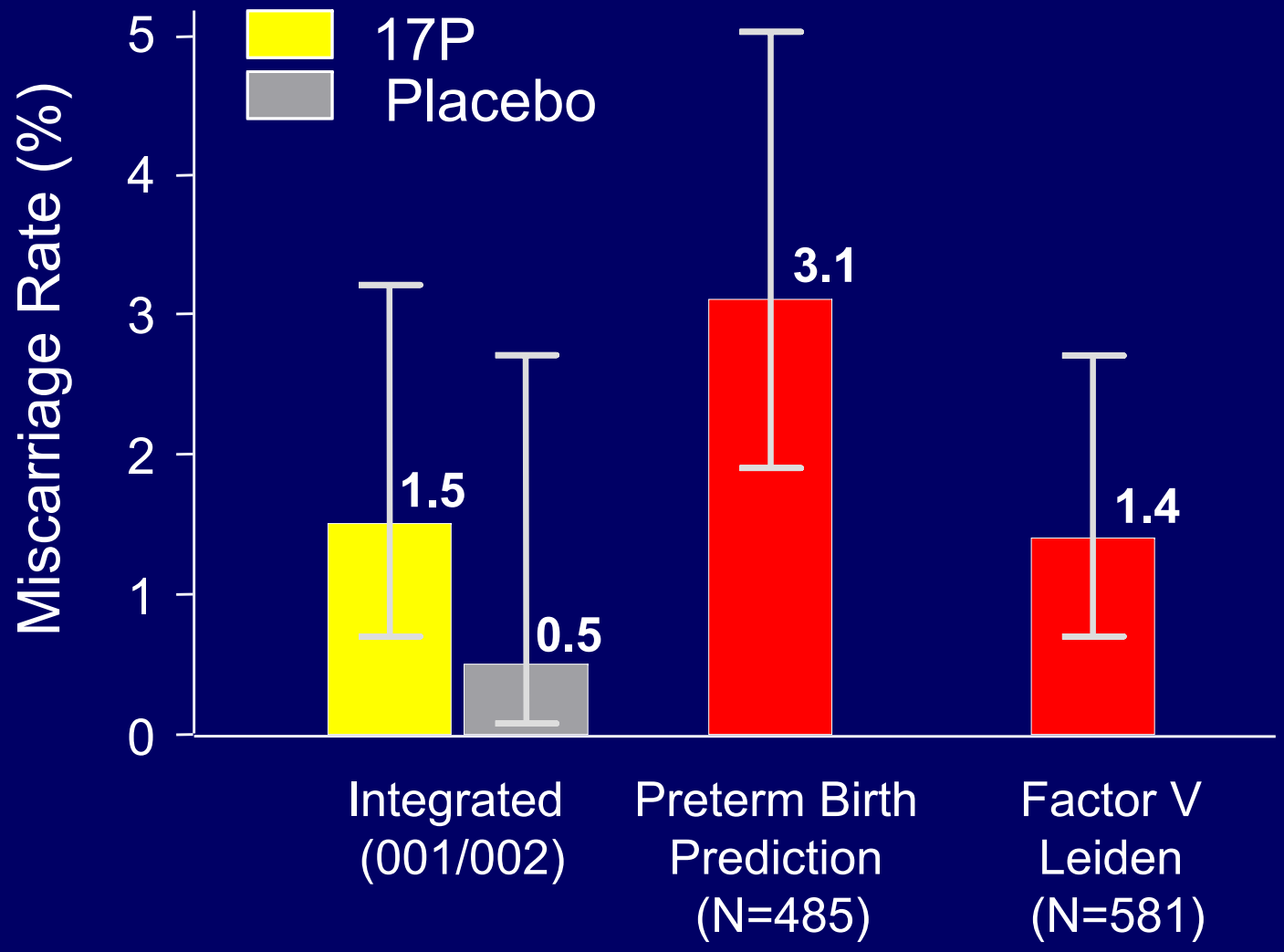
	17P (N=404) %	Placebo (N=209) %
Congenital anomalies	2.2	1.9
Musculoskeletal	0.7	1.0
Cardiovascular	0.5	0.5
Genitourinary	0.2	0.5
Male reproductive	0.5	0.5
Breast	0.2	0

Serious Adverse Events – Fetal/Neonatal Deaths

	17P (N=404) %	Placebo (N=209) %	P value
Miscarriages	1.5	0.5	0.2629
Stillbirths	1.7	1.9	0.8769
Neonatal deaths	2.5	4.3	0.1928

- No neonatal deaths, stillbirths, or miscarriages were considered related to study drug by investigators

Summary of Miscarriage Rates (16-20 Weeks) – NICHD Network Studies



17-HPC for Prevention of Miscarriage – Cochrane Database Review (2003)

- No difference between 17-HPC and Placebo
  - OR = 0.77 [0.36 – 1.68]
- Significant protective effect for progestins in women with ≥ 3 prior miscarriages
  - OR = 0.39 [0.17 - 0.91]
  - 3 studies, 1 of which used 17-HPC
- No difference for adverse effects on infant or mother

Oates-Whitehead RM et al. *Cochrane Database Syst Rev*. (4):CD003511; 2003

Safety Conclusions – Studies 002 and 001

The safety results demonstrate that weekly administration of 17P was

- Safe and well tolerated by pregnant women
- Safe for the developing fetus and neonate
  - Comparable rates of stillbirths, miscarriages, and neonatal deaths
  - Rates of congenital anomalies similar to general population rate of 2-3%

17P Follow-Up Study

- Assessed long-term impact of in utero exposure to 17P
  - Observational safety study
  - Based on surveys and physical examinations
- Enrolled 278 children born to women enrolled in Study 002
  - 17P Group – 194 infants (68% of births)
  - Placebo Group – 84 infants (59% of births)
- Age range from 30-64 months

Demographics
Follow-Up Study

	17P (N=194)	Placebo (N=84)
Age at enrollment (mo), mean (SD)	47.2 (8.6)	48.0 (8.3)
Gestational age at birth (wk), mean (SD)	37.3 (3.2)	36.2 (3.7)
Race/Ethnicity		
African American	54.1%	56.0%
Caucasian	28.4%	23.8%
Hispanic	14.9%	17.9%
Asian	1.0%	1.2%
Sex		
Male	58.2%	47.6%
Female	41.8%	52.4%

17P Follow-Up Study Components

- Based on surveys and physical examination
  - Ages and Stages Questionnaire
  - Survey Questionnaire
  - Physical Examination

Child Safety Assessments Follow-Up Study

- Ages and Stages Questionnaire (ASQ)
  - Widely used and validated screening tool
  - Identifies children at risk for developmental delay
    - Communication
    - Gross motor movement
    - Fine motor movement
    - Problem-solving
    - Personal-social

ASQ Sample Questions
3 Yr Old – Sample Questions

- Communication – ‘Does your child make sentences that are three or four words long?’
- Gross motor – ‘Does your child jump with both feet leaving the floor at the same time?’
- Fine motor – ‘Does your child thread a shoelace through either a bead or an eyelet of a shoe?’
- Problem-solving – ‘If your child wants something he cannot reach, does he find a chair or box to stand on to reach it?’
- Personal-social – ‘Can your child put on a coat, jacket or shirt by himself?’
- Overall – ‘Does anything about your child worry you?’
- Response options:
  - Yes
  - Sometimes
  - Not yet

ASQ Results

Area of Development	17P (N=193) %	Placebo (N=82) %	P value
Occurrence of score below cutoff on ≥1 area of development	27.5	28.0	0.9206
Communication	11.4	11.0	0.9191
Gross Motor	2.6	3.7	0.6989
Fine Motor	20.7	18.3	0.6445
Problem Solving	10.4	11.0	0.8797
Personal-Social	3.6	1.2	0.4427

- Conclusion: No differences observed between 17P and placebo

Child Safety Assessments Follow-Up Study

- Survey Questionnaire derived from
  - Preschool Activities Inventory
  - 2001 Child Health Supplement of the National Health Interview Survey
  - 1991 National Maternal and Infant Health Survey
  - Early Childhood Longitudinal Survey (Department of Education)
  - Avon Longitudinal Study of Parents and Children

Survey Questionnaire Sample Questions

- Communication/Problem Solving
  - 'Does (name) pronounce words, communicate with and understand others?'
- Motor Skills/Activity Level
  - 'Do you have any concerns about (name)'s overall activity level?'
- Overall Health
  - 'Does (name) have an impairment or health problem that limits his/her ability to walk, run or play?'
- Personal-Social
  - 'How often in the past month has he/she done the following?:
    played house, played ball games, played at fighting, played at being a mother or father, etc.'

Survey Questionnaire

- Survey Questionnaire results revealed no significant differences in
  - Physical growth
  - Motor skills/activity levels
  - Communication and problem solving
  - Overall health
  - Reported diagnoses by health professionals
  - Hearing, vision, and use of special equipment
  - Gender-specific play

Physical Examination

- General examination of body systems
- Documentation of any major abnormalities
- Specific identification of genital anomalies

Physical Examination Findings

Abnormality or Location of Abnormality	17P (N=194) %	Placebo (N=84) %
Skin	12.3	7.5
Inguinal nodes palpable	10.9	8.8
Mouth	9.1	8.6
Neck	5.9	4.9
Heart	5.3	0
Ears	3.2	3.7
Supraclavicular nodes palpable	3.3	2.5
Other syndromes or stigmata	2.7	5.1

Safety – Literature Review

- Epidemiological studies
  - Michaelis, West Germany (1983)
    - n = 462
  - Resseguie, Mayo Clinic (1985)
    - n = 649, 11.5 year mean follow-up
  - Katz, Israel (1985)
    - n = 1,608
- No association between 17-HPC exposure and congenital anomalies

FDA Assessment on Progestogen Class

- Background to the 1999 ruling noted

  "The reliable evidence, particularly from controlled studies, shows no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to progesterone or hydroxyprogesterone."

  From: FDA. 64 FR:17985 – 17988. April 13, 1999

Overall Safety Conclusions – NICHD Studies and Literature Review

17P considered safe based on:

- NICHD studies
  - Safe and well tolerated in pregnant women
  - Safe for the developing fetus and neonate based on
    - Comparable percentage of surviving offspring
    - Rates of congenital anomalies similar to general population rates of 2-3%
  - Safe for the child as evidenced by the lack of untoward effects on developmental milestones or physical health on follow-up safety assessments
- Literature review
- FDA assessment on progestogen class

Benefit / Risk

- Preterm birth is major unmet medical need
  - Leading cause of perinatal and neonatal mortality and morbidity
  - 33% increase in incidence of preterm birth since 1981
  - $26 billion annual cost associated with treating preterm infants
  - Staggering financial, social, and emotional costs associated with both early and late preterm birth

Benefit / Risk

- 17P has been shown to reduce the incidence of preterm birth
  - Significant efficacy demonstrated <37, <35, and <32 weeks of gestation
    - 32% reduction at <37 weeks
    - 31% reduction at <35 weeks
    - 39% reduction at <32 weeks
  - Results applicable irrespective of
    - Race of the mother
    - Number of previous preterm births
    - Gestational age of previous preterm birth

Benefit / Risk

- 17P treatment leads to healthier neonates
  - Lengthens mean gestational age at birth
  - Results in fewer infants under 2500 grams
    - 34% reduction
  - Reduces admissions to NICU
    - 24% reduction
  - Reduces important neonatal morbidities
    - Respiratory therapy
    - Necrotizing enterocolitis
    - Intraventricular hemorrhage

Benefit / Risk

- 17P administration was safe for pregnant women
  - Well tolerated
  - No increase in rates of complications or procedures
- No identified risk for fetus and neonate
  - Comparable rates of neonatal deaths, miscarriages, and stillbirths
  - No evidence of teratogenicity
    - Congenital anomalies at similar rates
    - Confirmed by 1999 FDA assessment
    - Second trimester administration
- No identified risk for the child
  - No association with developmental delays or other issues in children between 30 and 64 months of age

Proposed Indication

"Gestiva is indicated for the prevention of preterm birth in pregnant women with a history of at least one spontaneous preterm birth."

All Back Up Slides Presented During Q&A

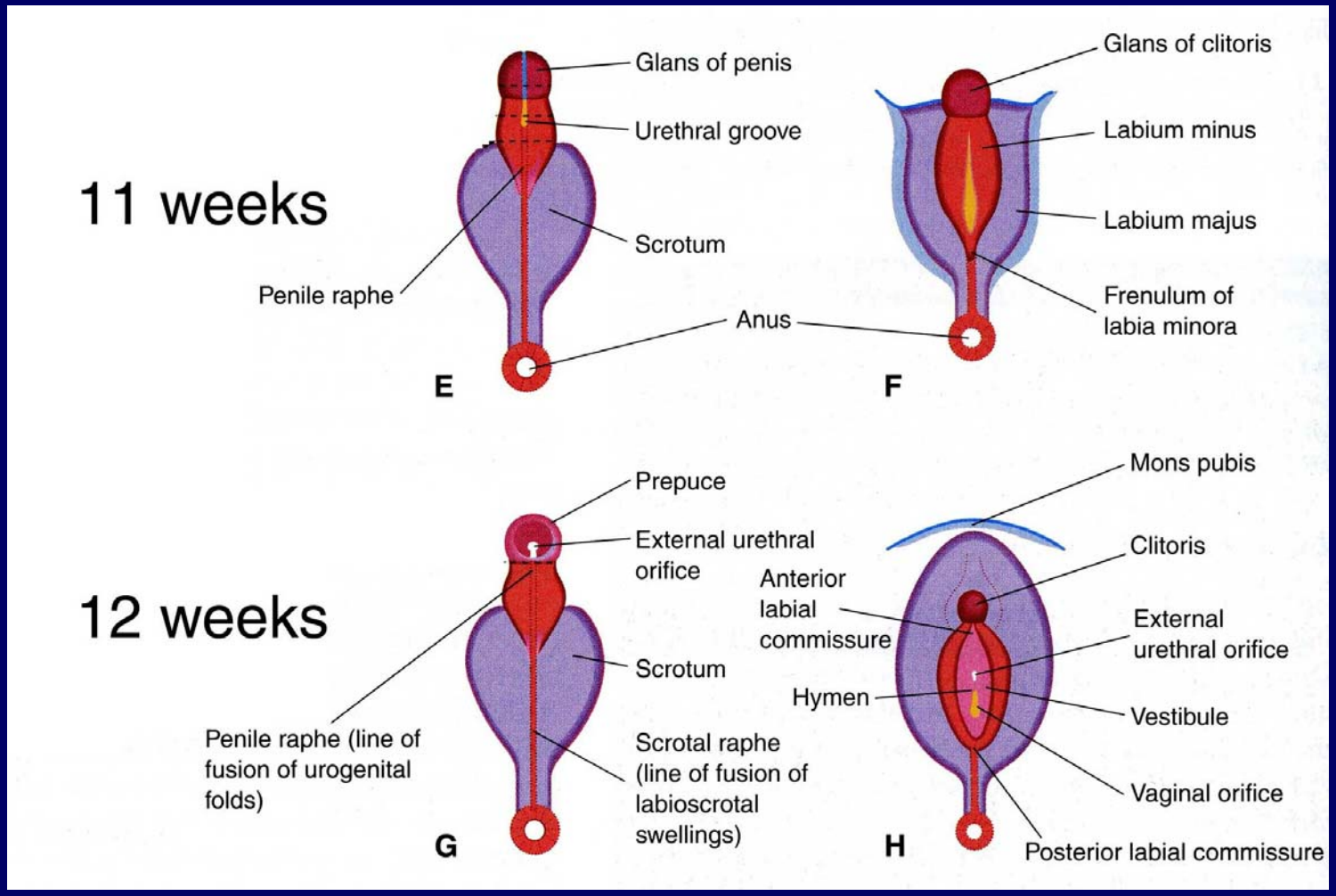
Not in any specific order

Hochberg* Adjustment for Multiple Comparisons

Outcome	P value	Rank	Statistically significant	Adjusted P value
PTD <32	0.027	1	Yes	0.027
PTD <35	0.026	2	Yes	0.027
PTD <37	0.0003	3	Yes	0.0009

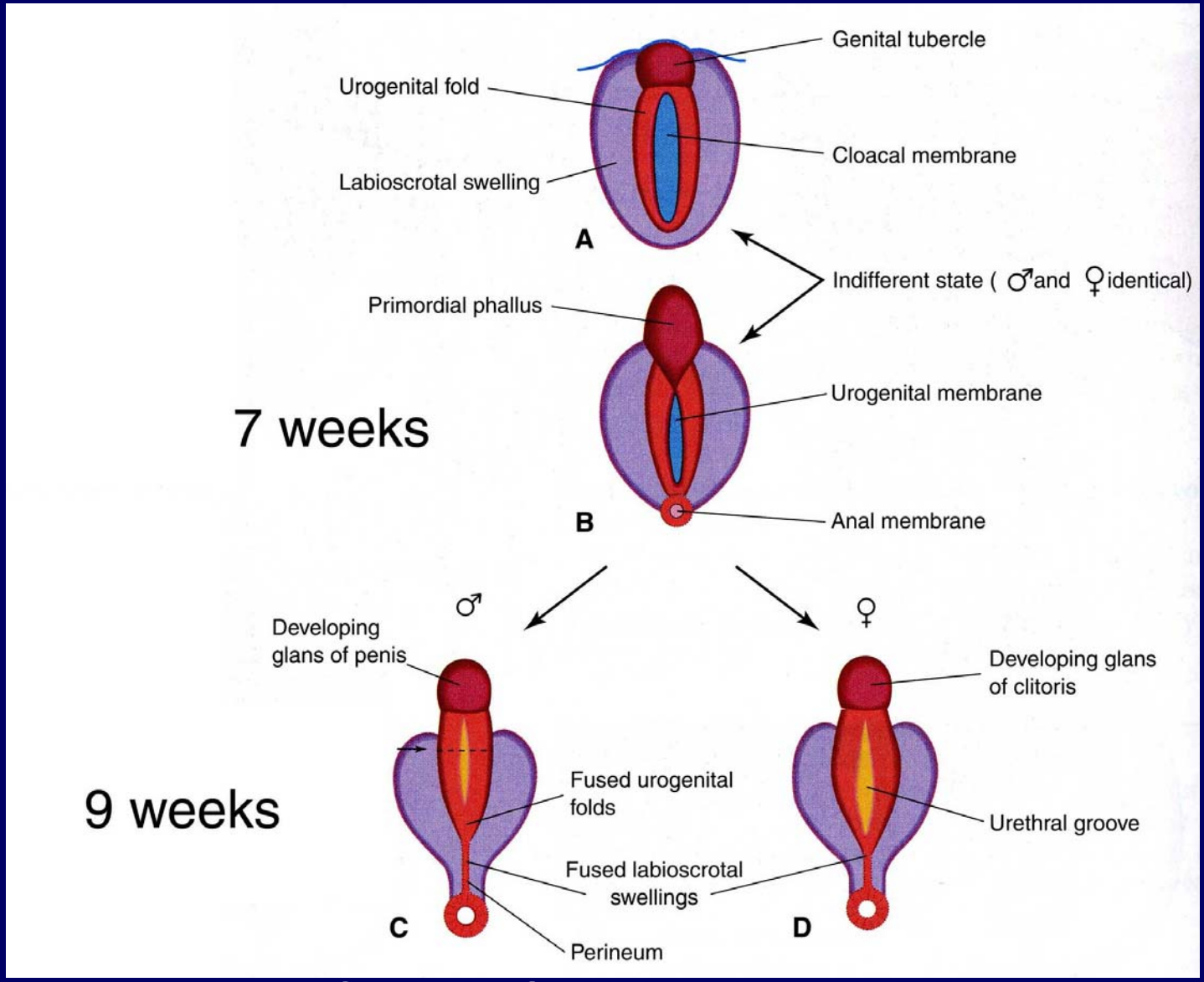
*Hochberg Y., Biometrica (1988)

Development of the External Genitalia (2 of 2)



The Developing Human: Clinically Oriented Embryology, Moore, Persaud 2003

Development of the External Genitalia (1 of 2)



The Developing Human: Clinically Oriented Embryology, Moore, Persaud 2003

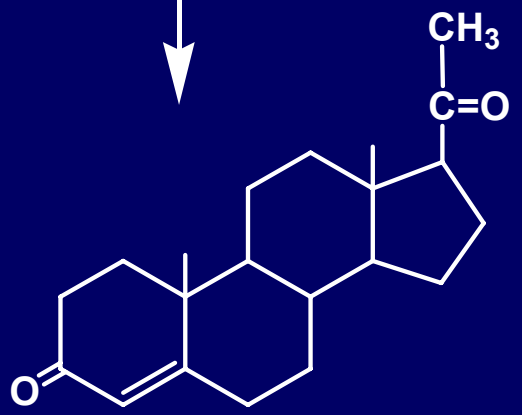
Unlike Progesterone, 17-HPC Is Not Converted to Androgens, Estrogens or Corticosteroids

17-HPC

Androgens

Estrogens

Corticosteroids



Progesterone

Androgens

Estrogens

Corticosteroids

Bacterial Vaginosis During Pregnancy vs Outcome

	17P N=64	Placebo N=24
Miscarriage	1 (1.6%)	0 (0%)
Stillborn	2 (3.1%)	1 (4.2%)
pPROM <37	6 (9.4%)	7 (29.2%)
Neonatal Sepsis[a]	2 (3.3%)	0 (0%)
Cerebral palsy[b]	0/46 (0)	0/16 (0)

[a] based on livebirths

[b] Based on 62 children enrolled in the Follow-up Study

Preterm Birth <37 in Patients with Bacterial Vaginosis

	17P n/N (%)	Placebo n/N (%)
Preterm birth <37 weeks		
No bacterial vaginosis	88/246 (35.8)	67/129 (51.9)
Bacterial vaginosis	27/64 (42.2)	17/24 (70.8)

Reasons for Oral Metronidazole Use

	17P (N=32) n %	Placebo (N=8) n %
Bacterial vaginosis	25 (78.1)	6 (75.0)
Trichomonas	10 (31.3)	2 (25.0)
Other vaginal/cervical infection	0 (0)	1 (12.5)

Note: 2 patients in the 17P group and 1 patient in the placebo group had both bacterial vaginosis and trichomonas

Use of Metronidazole

	17P (N=310) n %	Placebo (N=153) n %
Oral	32 (10.3)	8 (5.2)
Vaginal	1 (0.3)	1 (0.7)
Any use	33 (10.7)	9 (5.9)

Incidence of BV

	17P (N=310) n %	Placebo (N=153) n %
Prior to randomization	41 (13.2)	20 (13.1)
Randomization through delivery	27 (8.7)	8 (5.2)
At any time during pregnancy	64 (20.7)	24 (15.7)

Note: 4 patients in each group has BV prior to randomization and from randomization through delivery

Chorioamnionitis at Delivery

	17P N=399 n (%)	Placebo N=205 n (%)	P value
Confirmed clinical chorioamnionitis	13 (3.3)	5 (2.4)	0.8011

Infections – BV and Trichomonas

- Collected on CRF at 2 time points:
  - At baseline, patient report and record review
  - During study, the CRF for “Record of Antibiotic Use” included the reason for administration of antibiotic
- Clinical chorioamnionitis
  - Collected on the labor and delivery summary CRF
- Diagnosed by treating physician based on methods and criteria based at the local site

Gestational Diabetes – Summary

- Gestational diabetes following randomization was not statistically different (P=0.179)
  - 17P = 6.3%
  - Placebo = 3.4%
- Gestational diabetes rate reported by the American Diabetes Association ~ 7%
- Progestins may disturb glucose homeostasis
  - Rates of gestational diabetes in this study were similar to ADA

Gestational Diabetes – Integrated Studies

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	25/382 (6.5)	7/200 (3.5)

***Number of women without a history of diabetes at baseline**

Diabetes – Study 001

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	8/89 (9.0)	0/52 (0)

***Number of women without a history of diabetes at baseline**

Diabetes Study 002

Rate of Gestational Diabetes

	17P n/N* (%)	Placebo n/N* (%)
No history of diabetes	17/293 (5.8)	7/148 (4.7)

*Number of women without a history of diabetes at baseline

Prevention of Preterm Birth Integrated Results

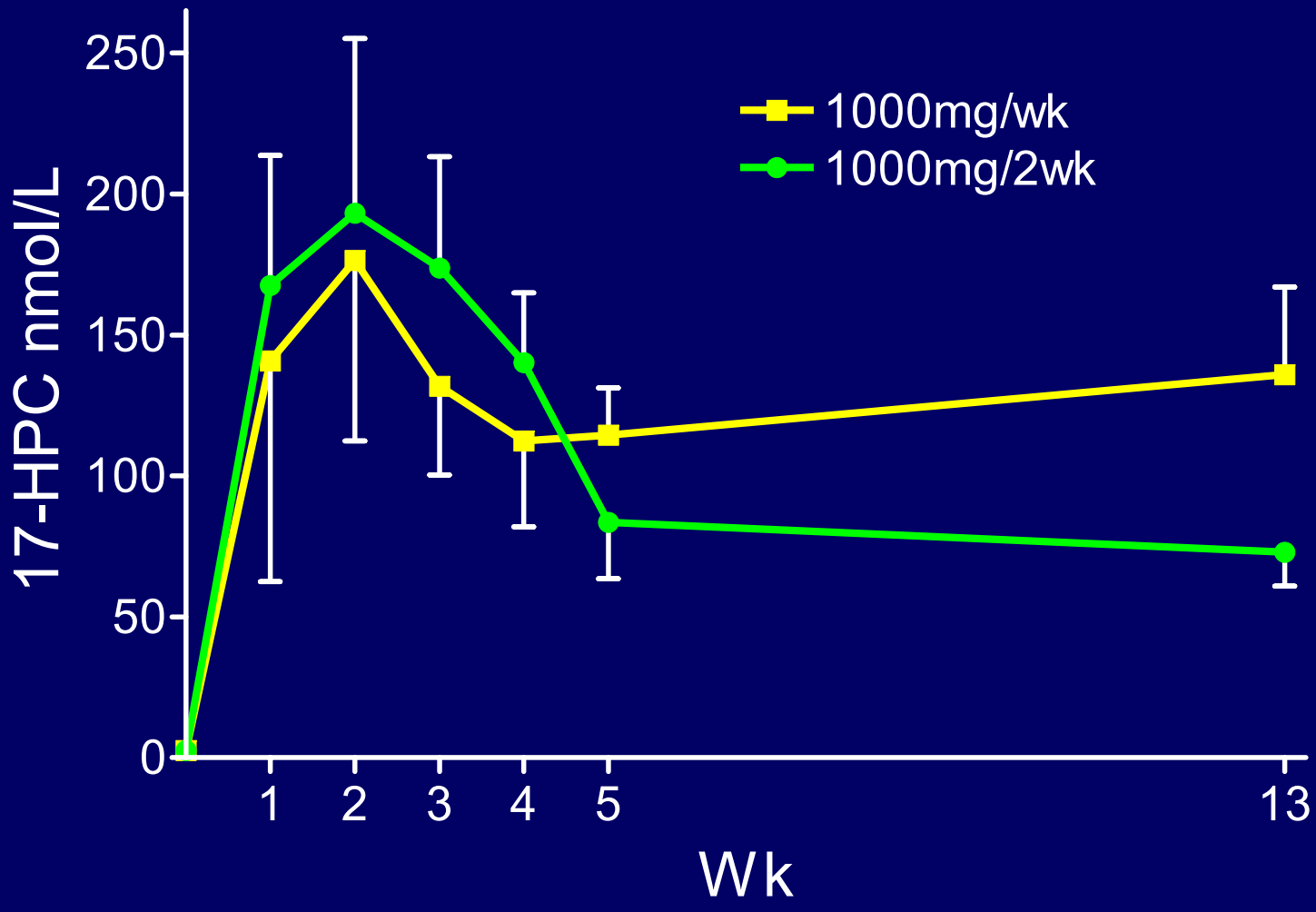
Pregnancy Outcome	17P (N=404) %	Placebo (N=209) %	P value
Birth <37^0 weeks	38.1	49.8	0.0052 0.0155[a]
Birth <35^0 weeks	22.0	30.6	0.0211
Birth <32^0 weeks	12.4	18.7	0.0367

[a]P value from a logistic regression adjusting for the number of previous preterm deliveries

Composition of Injectable Formulations of 17-HPC

Component	Adeza Product	Study 17P-CT-002	Delalutin, 250 mg/mL
17-HPC	250 mg/mL	250 mg/mL	250 mg/mL
Benzyl benzoate	46%	46%	46%
Benzyl alcohol	2%	2%	2%
Castor oil	q.s. to volume	q.s. to volume	q.s. to volume

Multiple-Dose Pharmacokinetic Profile



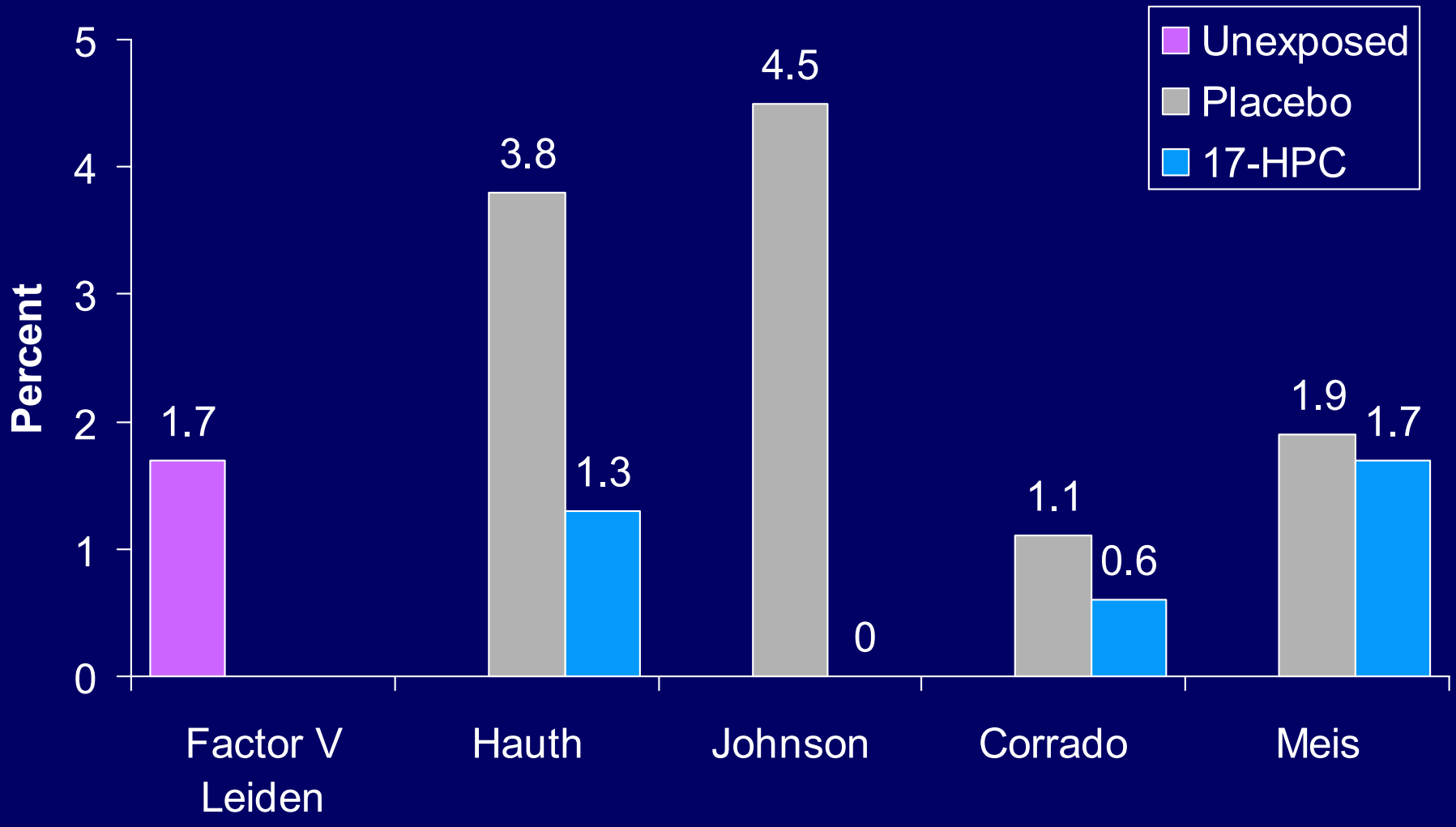
Serum concentrations of HPC in patients who after a loading dose of 1000 mg daily for 5 days were treated with either 1000 mg HPC every week or with 1000 mg every 2 weeks

From Onsrud, 1985

Tocolytic Use – Study 002

	17P (N=310) %	Placebo (N=153) %
Tocolytic use	12.9	11.8

Stillbirth Rates



Stillbirths – Study 001/002

	17P (N=404) n (%)	Placebo (N=209) n (%)	P value
Stillbirths	7 (1.7)	4 (1.9)	0.8769
Antepartum	6	2	
Intrapartum	1	2	

Cardiac Findings – Summary

- Low rate of cardiac anomalies observed at birth in both 17P and placebo groups (0.5% vs 0.5%)
- Patent ductus arteriosus observed in 2.4% of 17P cases and 5.4% of placebo cases
- At Follow-Up Study examination
  - Infants in the 17P
    - Murmurs – 4.6%
    - Irregular rhythm – 0.5%
  - No functional disabilities noted by history or physical exam

Corticosteroid Use At Baseline – Study 002

	17P (N=310) n (%)	Placebo (N=153) n (%)	P value
Any corticosteroid use (before randomization)	5 (1.6%)	8 (5.2%)	0.0324
Inhaled corticosteroid use	1 (0.3)	7 (4.6)	

Corticosteroids Use

- Time points for data collection
  - At baseline
  - Weekly during prenatal visits
  - Preterm labor admissions
- Corticosteroid use collected only prior to the birth hospitalization
- No specific guidelines were given to site investigators regarding use

Kester – Effects of Prenatal 17-HPC on Adolescent Males (1984)

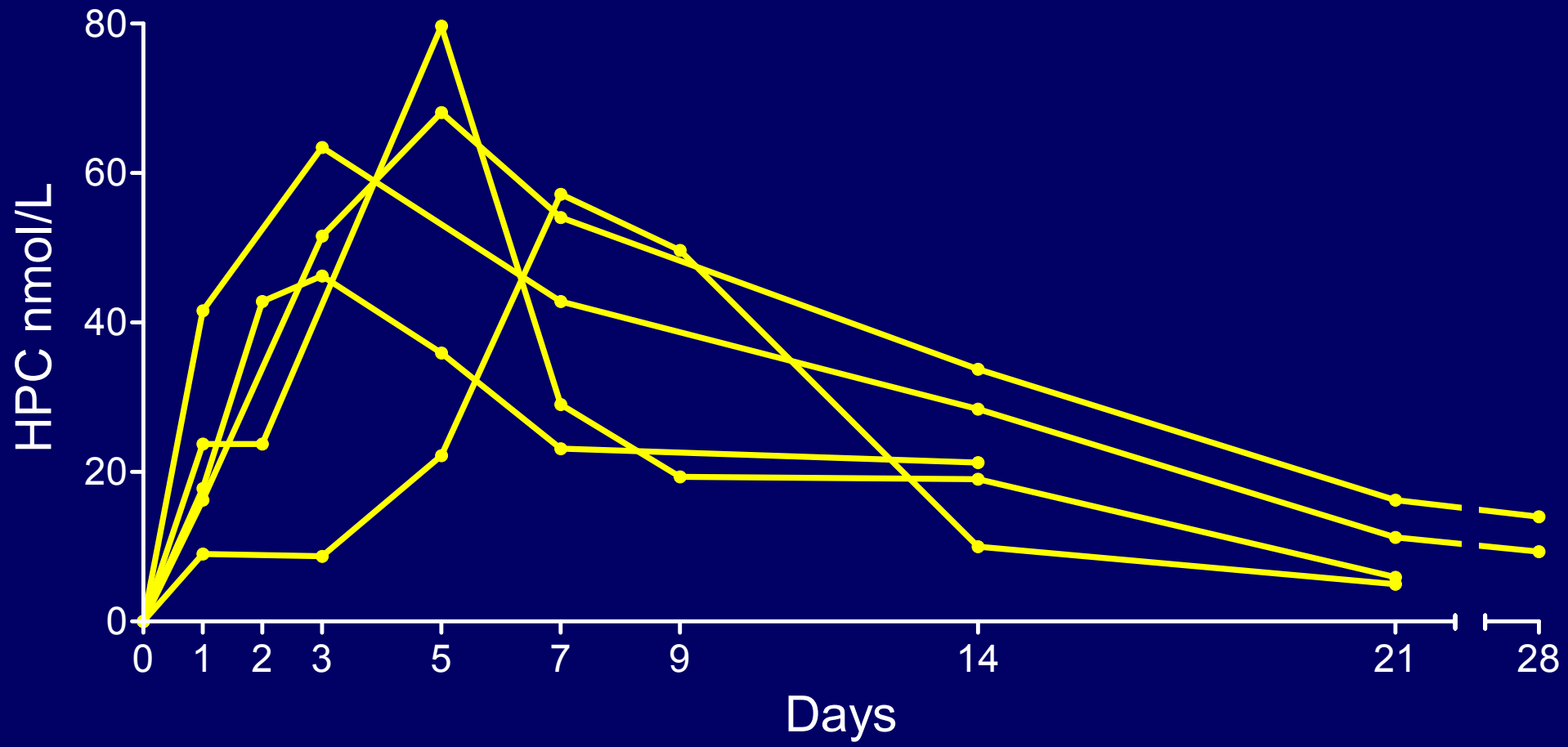
- Examined 25 adolescent males exposed to 17-HPC prenatally
- Assessed impact on recreational interests and psychosexual development in boyhood
- No difference in psychological testing noted between adolescents exposed to 17-HPC and unexposed controls
- No impact on results based on total dosage of 17-HPC, duration of exposure, or period of gestation

Kester PA. *Arch Sex Behav*. 1984;13(5):441-55

Table 4-10. Neonatal Morbidity and Mortality for Live Births (1 of 2)

Morbidity	17P N=295 n (%)	Placebo N=151 n (%)	P value
Transient tachypnea	11 (3.7)	11 (7.3)	0.0990
Respiratory distress syndrome (RDS)	29 (9.9)	23 (15.3)	0.0900
Bronchopulmonary dysplasia (BPD)	4 (1.4)	5 (3.3)	0.1730
Persistent pulmonary hypertension	2 (0.7)	1 (0.7)	1.0000
Ventilator support	26 (8.9)	22 (14.8)	0.0616
Supplemental oxygen	45 (15.4)	36 (24.2)	0.0248
Patent ductus arteriosus	7 (2.4)	8 (5.4)	0.1004
Seizures	3 (1.0)	0	0.5541
Any intraventricular hemorrhage (IVH)	4 (1.4)	8 (5.3)	0.0258
Grade 3 or 4 IVH	2 (0.7)	0	0.5511
Other intracranial hemorrhage	1 (0.3)	2 (1.3)	0.2628

Plasma Concentrations of 17-HPC over Time



Individual serum concentrations of HPC in 5 patients after intramuscular administration of a single dose of 1000 mg (arrow)

From Onsrud, 1985

Single Dose Pharmacokinetics of 17-HPC (1000 mg)

Parameter	Mean ± SD	n
C_{max} (ng/mL)	27.8 ± 5.3	5
T_{max} (days)	4.6 ± 1.7	5
$t_{1/2}$ (days)	7.8 ± 3.0	4
AUC_{0-7} (ng•day/mL)	118 ± 36	5
$AUC_{0-\infty}$ (ng•day/mL)	355 ± 136	4

From Onsrud, 1985

17-HPC Teratogenicity Data in Mice

- No teratogenicity or maternal toxicity observed
  - C57Bl/6J Mice exposed to 0.5, 5, and 50 mg/kg/d (0.1-10 X clinical dose) via subdermal pellets on gestation d 7-19 (n=8)[1]
- No teratogenicity observed
  - ARS Swiss Webster Mice exposed to 42, 416, and 833 mg/kg (~10-200 X clinical dose) on d 6-15; n=11-15[2]; SC

[1]Carbone 1993

[2]Seegmiller, 1983

17-HPC Teratogenicity Data in Rhesus and Cynomolgus Monkeys

- No drug related anomalies found in fetuses from either species of monkey
- Treatment initiated much earlier in gestation (first third) than what is indicated in humans (16-20 weeks)[1]
- No teratogenicity in Rhesus monkeys[2]

[1]Hendrickx *et al.* 1987

[2]Courtney and Valerio, 1968

17-HPC Mechanism of Action

- In vitro receptor binding studies show 17-HPC:
  - Better than either progesterone or 17-α-hydroxyprogesterone at inducing progesterone-responsive gene transcription[1]
  - Comparable to progesterone in binding affinity for progesterone receptor[2]
  - Displays greater selectivity for receptor isoform B (transcriptional activator) compared to isoform A (transcriptional repressor)

[1]Zeleznik et al. (abstract), 2006

[2]Attardi et al. (abstract), 2006

Proposed Genomic and Nongenomic Mechanisms of Progesterone

- Modulates progesterone receptor activity
- Reduces estrogen receptor activity
- Blocks oxytocin induced uterine contractility
- Enhances tocolytic response
- Promotes local antiinflammatory effects
- Inhibits myometrial gap junctions

Study 002 and HUAM Study: Sample Size Considerations

	Study 002	HUAM Study
1 previous PTD	314 (67.8%)	194 (76.4%)
>1 previous PTD	149 (32.2%)	57 (22.4%)
GA of worst previous PTB, mean (SD)	29.7 (4.9)	30.2 (4.9)
GA qualifying delivery (wk), mean (SD)	30.8 (4.5)	ND
Year completed	2002	1996
MFMU Sites	19	11
Design	Interventional	Observational

17-HPC Mechanism of Action

- Not known
  - Multiple pathways possible
- May be distinct from progesterone, though pharmacologically similar
- Progesterone inhibits myometrial contractility through
  - Non-genomic mechanisms
  - Genomic mechanisms

Study 002: Preterm Birth <37^0 by Site

Center	17P n/N	(%)	Placebo n/N	(%)
2 – Pittsburgh	5/24	(20.8)	11/12	(91.7)
4 – Tennessee	13/30	(43.3)	9/15	(60.0)
8 – Alabama	23/86	(26.7)	18/40	(45.0)
9 – Detroit	5/16	(31.3)	5/8	(62.5)
11 – Cincinnati	3/9	(33.3)	2/4	(50.0)
13 – Wake Forest	7/13	(53.9)	7/9	(77.8)
15 – Ohio State	11/20	(55.0)	4/8	(50.0)
18 – Dallas	12/28	(42.9)	8/11	(72.7)
20 – Utah	11/29	(37.9)	7/14	(50.0)
21 – Philadelphia	10/17	(58.8)	3/7	(42.9)
22 – Providence	1/3	(33.3)	1/2	(50.0)
23 – New York	2/6	(33.3)	1/5	(20.0)
25 – Cleveland	2/4	(50.0)	1/2	(50.0)
26 – Houston and 19 – San Antonio	3/10	(30.0)	4/7	(57.1)
27 – Chapel Hill and 17 – Miami	3/9	(33.3)	1/6	(16.7)
28 – Chicago and 14 – Chicago	4/6	(66.7)	2/3	(66.7)

Study 002: Secondary Pregnancy Outcomes

Pregnancy Outcome	17P N=310 n (%)	Placebo N=153 n (%)	P value
Delivery <35^0	67 (21.6)	47 (30.7)	0.0324
Delivery <32^0	39 (12.6)	30 (19.6)	0.0458
Spontaneous delivery <37^0	94 (30.3)	69 (45.1)	0.0017
SPTD <37^0 due to pPROM	26 (8.4)	16 (10.5)	0.4656
SPTD <37^0 due to PTL	67 (21.6)	53 (34.6)	0.0026
SPTD <37^0 due to PTL or pPROM	89 (28.7)	69 (45.1)	0.0005
Indicated delivery <37^0	25 (8.1)	15 (9.8)	0.5309

Genital/Reproductive Abnormalities

- Micropenis (17P)
  - Born at 38^{1} weeks gestation
  - Aged 4.5 years at Follow-Up Study exam
  - Genital exam at birth – normal
- Micropenis (17P)
  - Born at 33^{5} weeks gestation
  - Aged 3.5 years at Follow-Up Study exam
  - Infant with Down syndrome
  - Common associated finding

Genital/Reproductive Abnormalities

- Early puberty (17P)
  - Born at 39^{6} weeks gestation
  - Aged 3.6 years at Follow-Up Study exam
  - Breast buds observed at Follow-Up Study exam
  - Obese female child
    - 66 lbs (100^{th} percentile BMI)
- Sparse pubic hair (Placebo)
  - Born at 25^{1} weeks gestation
  - Aged 3.5 years at Follow-Up Study exam
  - “Four or five long pubic hairs” at Follow-Up Study exam
  - No other abnormalities noted

Reproductive & Genitourinary Anomalies

- Infant 020-023 (17P)
  - Born at 38^{1} weeks gestation
  - Aged 5 years at Follow-Up Study exam
  - Labia “fused together” at Follow-Up Study exam
  - Genital exam at birth – normal
  - Multiple infant exams between 1 week and 3 years with normal exams
  - Urogenital sinus fuses at 12 weeks of gestation
  - Represents benign labial adhesions rather than labioscrotal fusion

Reproductive & Genitourinary Anomalies

- Infant 018-032
  - Born at 38^{1} weeks gestation
  - Aged 4 years at Follow-Up Study exam
  - Genital exam at birth – normal
  - Infant was reexamined 4 months later
    - Same examiner
    - Reported to be normal
    - “Clitoris <5mm in transverse diameter”

Physical Examination – Genital Abnormalities

- Genital/reproductive abnormalities
  - 17P group – 1.5%
  - Placebo group – 1.2%
- Abnormalities identified were
  - Breast buds
    - 17P female, 100% BMI
  - Sparse pubic hair
    - Placebo female, no other abnormalities
  - Micropenis
    - 17P male, genital exam at birth, normal
    - 17P male, Down syndrome