UT Southwestern Medical Center

Prevention of preterm birth I: Progestogen therapy

David B. Nelson, MD
Gillette Professorship of Obstetrics and Gynecology
Dedman Family Scholar in Clinical Care
Chief, Division of Maternal-Fetal Medicine
Associate Professor, Maternal-Fetal Medicine
Department of Obstetrics & Gynecology
University of Texas Southwestern Medical Center

UT Southwestern
Medical Center

~~Prevention of preterm birth I:~~ ~~Progestogen therapy~~

"The long and winding road of progestogen use for prevention of recurrent preterm birth"

David B. Nelson, MD
Gillette Professorship of Obstetrics and Gynecology
Dedman Family Scholar in Clinical Care
Chief, Division of Maternal-Fetal Medicine
Associate Professor, Maternal-Fetal Medicine
Department of Obstetrics & Gynecology
University of Texas Southwestern Medical Center

Disclosures

- No personal disclosures or conflicts of interest for this presentation.

- Portions of the data presented were funded by: National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR001105.

Objectives

1. Outline the burden of preterm birth.

2. Chronicle the use of progestogens in preterm birth prevention.

3. Review local experiences with progestogens relative to national practices.

Covering 50+ years in 45 min!

Burden of preterm birth

Current Rates of Preterm Birth: Global

National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis

Eric O Ohuma, Ann-Beth Moller*, Ellen Bradley*, Samuel Chakwera, Laith Hussain-Alkhateeb, Alexandra Lewin, Yemisrach B Okwaraji, Wahyu Retno Mahanani, Emily White Johansson, Tina Lawin, Diana Estevez Fernandez, Giovanna Gatica Domínguez, Ayesha de Costa, Jenny A Cresswell, Julia Krasevec, Joy E Lawn, Hannah Blencowe†, Jennifer Requejo†, Allisyn C Moran†*

Summary

Background Preterm birth is the leading cause of neonatal mortality and is associated with long-term physical, neurodevelopmental, and socioeconomic effects. This study updated national preterm birth rates and trends, plus novel estimates by gestational age subgroups, to inform progress towards global health goals and targets, and aimed to update country, regional, and global estimates of preterm birth for 2020 in addition to trends between 2010 and 2020.

Methods We systematically searched population-based, nationally representative data on preterm birth from Jan 1, 2010, to Dec 31, 2020 and study data (26 March–14 April, 2021) for countries and areas with no national-level data. The analysis included 679 data points (86% nationally representative administrative data [582 of 679 data points]) from 103 countries and areas (62% of countries and areas having nationally representative administrative data [64 of 103 data points]). A Bayesian hierarchical regression was used for estimating country-level preterm rates, which incoporated country-specific intercepts, low birthweight as a covariate, non-linear time trends, and bias adjustments based on a data quality categorisation, and other indicators such as method of gestational age estimation.

Findings An estimated 13·4 million (95% credible interval [CrI] 12·3–15·2 million) newborn babies were born preterm (<37 weeks) in 2020 (9·9% of all births [95% CrI 9·1–11·2]) compared with 13·8 million (12·7–15·5 million) in 2010 (9·8% of all births [9·0–11·0]) worldwide. The global annual rate of reduction was estimated at −0·14% from 2010 to 2020. In total, 55·6% of total livebirths are in southern Asia (26·8% [36 099 000 of 134 767 000]) and sub-Saharan Africa (28·7% [38 819 300 of 134 767 000]), yet these two regions accounted for approximately 65% (8 692 000 of 13 376 200) of all preterm births globally in 2020. Of the 33 countries and areas in the highest data quality category, none were in southern Asia or sub-Saharan Africa compared with 94% (30 of 32 countries) in high-income countries and areas. Worldwide from 2010 to 2020, approximately 15% of all preterm births occurred at less than 32 weeks of gestation, requiring more neonatal care (<28 weeks: 4·2%, 95% CI 3·1–5·0, 567 800 [410 200–663 200 newborn babies]); 28–32 weeks: 10·4% [9·5–10·6], 1 392 500 [1 274 800–1 422 600 newborn babies]).

Interpretation There has been no measurable change in preterm birth rates over the last decade at global level. Despite increasing facility birth rates and substantial focus on routine health data systems, there remain many missed opportunities to improve preterm birth data. Gaps in national routine data for preterm birth are most marked in regions of southern Asia and sub-Saharan Africa, which also have the highest estimated burden of preterm births. Countries need to prioritise programmatic investments to prevent preterm birth and to ensure evidence-based quality care when preterm birth occurs. Investments in improving data quality are crucial so that preterm birth data can be improved and used for action and accountability processes.

Funding The Children's Investment Fund Foundation and the UNDP, United Nations Population Fund-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

Introduction

Preterm birth (<37 weeks of gestation) is a global burden considered to be one of the main risk factors for neonatal mortality (aged under 5 years) and is associated with short-term and long-term effects, such as poor health and growth, intellectual and mental disabilities, and early onset of chronic diseases, among others.[1–3] Previous estimates showed that 10·6% (uncertainty interval: 9·0–12·0%, 14·84 million [12·65 million–16·73 million]) of all livebirths worldwide were preterm births in 2014.[4]

Lancet 2023; 402: 1261–71

See Comment page 1215

*Joint first authors
†Joint senior authors

Maternal, Adolescent, Reproductive and Child Health (MARCH) Centre (E O Ohuma PhD, E Bradley MSc, Y B Okwaraji PhD, J E Lawn PhD, H Blencowe PhD) and Department of Medical Statistics (A Lewin PhD), London School of Hygiene & Tropical Medicine, London, UK; Human Reproduction Programme (the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland (A-B Moller MPH, T Lawin PhD, J A Cresswell PhD); Department of Data and Analytics (W R Mahanani MSc), Division of Data, Analytics and Delivery for Impact (D E Fernandez MSc), World Health Organization, Geneva, Switzerland; Department of Maternal, Newborn, Child and Adolescent Health and Ageing (A de Costa MD, A C Moran PhD) and Department of Nutrition and Food Safety (G G Domínguez PhD), World Health Organization, Geneva, Switzerland; Division of Data, Analytics, Planning and Monitoring, United Nations Children's Fund, New York, NY, USA (S Chakwera MSc, J Krasevec MSc, J Requejo PhD); Global Health, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (L Hussain-Alkhateeb PhD); Department of Women and Children's Health, Uppsala University, Uppsala, Sweden (E W Johansson PhD)

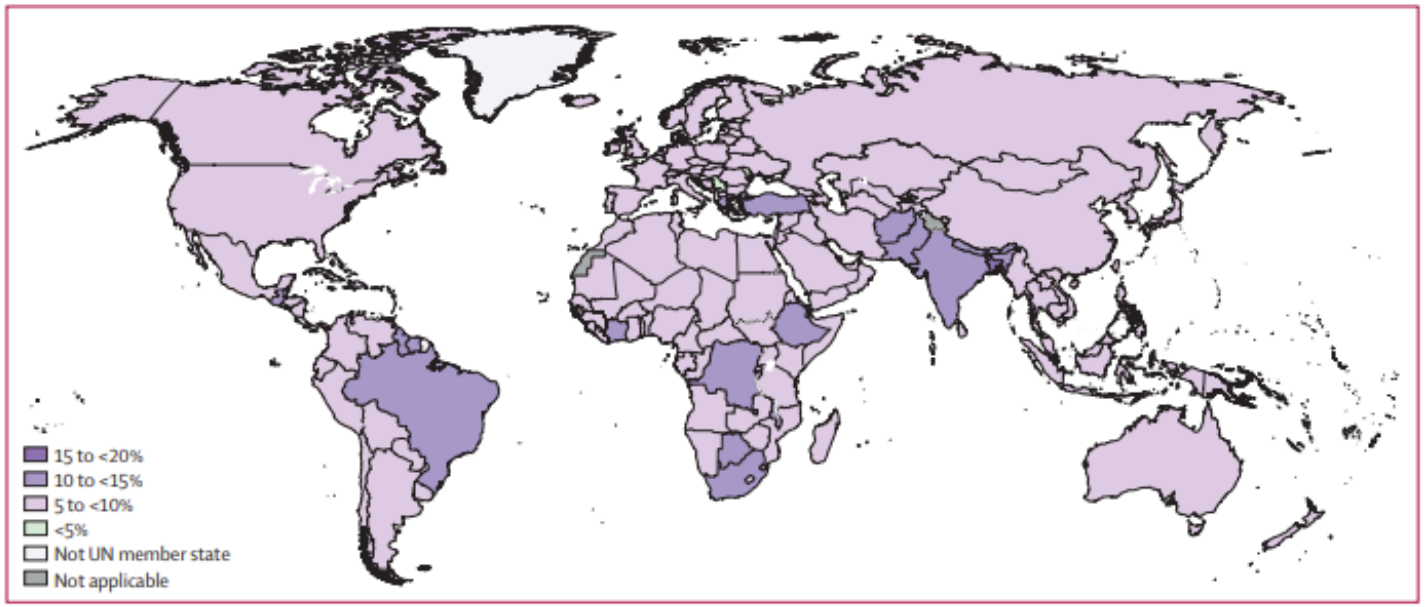


Figure 2: **Estimated national preterm birth rates in 2020**
The boundaries shown on this map do not signify any official endorsement of borders, or the legal status of any country or area. Produced by WHO.

Ohuma EO, et al. Lancet. 2023

UT Southwestern Medical Center

Current Rates of Preterm Birth: Global

National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis

Eric O Ohuma*, Ann-Beth Moller*, Ellen Bradley*, Samuel Chakwera, Laith Hussain-Alkhateeb, Alexandra Lewin, Yemisrach B Okwaraji, Wahyu Retno Mahanani, Emily White Johansson, Tina Lawin, Diana Estevez Fernandez, Giovanna Gatica Domínguez, Ayesha de Costa, Jenny A Cresswell, Julia Krasevec, Joy E Lawn, Hannah Blencowe†, Jennifer Requejo†, Allisyn C Moran†

Summary

Background Preterm birth is the leading cause of neonatal mortality and is associated with long-term physical, neurodevelopmental, and socioeconomic effects. This study updated national preterm birth rates and trends, plus novel estimates by gestational age subgroups, to inform progress towards global health goals and targets, and aimed to update country, regional, and global estimates of preterm birth for 2020 in addition to trends between 2010 and 2020.

Methods We systematically searched population-based, nationally representative data on preterm birth from Jan 1, 2010, to Dec 31, 2020 and study data (26 March–14 April, 2021) for countries and areas with no national-level data. The analysis included 679 data points (86% nationally representative administrative data [582 of 679 data points]) from 103 countries and areas (62% of countries and areas having nationally representative administrative data [64 of 103 data points]). A Bayesian hierarchical regression was used for estimating country-level preterm rates, which incoporated country-specific intercepts, low birthweight as a covariate, non-linear time trends, and bias adjustments based on a data quality categorisation, and other indicators such as method of gestational age estimation.

Findings An estimated 13·4 million (95% credible interval [CrI] 12·3–15·2 million) newborn babies were born preterm (<37 weeks) in 2020 (9·9% of all births [95% CrI 9·1–11·2]) compared with 13·8 million (12·7–15·5 million) in 2010 (9·8% of all births [9·0–11·0]) worldwide. The global annual rate of reduction was estimated at −0·14% from 2010 to 2020. In total, 55·6% of total livebirths are in southern Asia (26·8% [36 099 000 of 134 767 000]) and sub-Saharan Africa (28·7% [38 819 300 of 134 767 000]), yet these two regions accounted for approximately 65% (8 692 000 of 13 376 200) of all preterm births globally in 2020. Of the 33 countries and areas in the highest data quality category, none were in southern Asia or sub-Saharan Africa compared with 94% (30 of 32 countries) in high-income countries and areas. Worldwide from 2010 to 2020, approximately 15% of all preterm births occurred at less than 32 weeks of gestation, requiring more neonatal care (<28 weeks: 4·2%, 95% CI 3·1–5·0, 567 800 [410 200–663 200 newborn babies]); 28–32 weeks: 10·4% [9·5–10·6], 1 392 500 [1 274 800–1 422 600 newborn babies]).

Interpretation There has been no measurable change in preterm birth rates over the last decade at global level. Despite increasing facility birth rates and substantial focus on routine health data systems, there remain many missed opportunities to improve preterm birth data. Gaps in national routine data for preterm birth are most marked in regions of southern Asia and sub-Saharan Africa, which also have the highest estimated burden of preterm births. Countries need to prioritise programmatic investments to prevent preterm birth and to ensure evidence-based quality care when preterm birth occurs. Investments in improving data quality are crucial so that preterm birth data can be improved and used for action and accountability processes.

Funding The Children's Investment Fund Foundation and the UNDP, United Nations Population Fund-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction.

Introduction

Preterm birth (<37 weeks of gestation) is a global burden considered to be one of the main risk factors for neonatal mortality (aged under 5 years) and is associated with short-term and long-term effects, such as poor health and growth, intellectual and mental disabilities, and early onset of chronic diseases, among others.[1–3] Previous estimates showed that 10·6% (uncertainty interval: 9·0–12·0%, 14·84 million [12·65 million–16·73 million]) of all livebirths worldwide were preterm births in 2014.[4]

Lancet 2023; 402: 1261–71
See Comment page 1215

*Joint first authors
†Joint senior authors
Maternal, Adolescent, Reproductive and Child Health (MARCH) Centre (E O Ohuma PhD, E Bradley MSc, Y B Okwaraji PhD, J E Lawn PhD, H Blencowe PhD) and Department of Medical Statistics (A Lewin PhD), London School of Hygiene & Tropical Medicine, London, UK; Human Reproduction Program (the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction), Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland (A-B Moller MPH, T Lavin PhD, J A Cresswell PhD); Department of Data and Analytics (W R Mahanani MSc), Division of Data, Analytics and Delivery for Impact (D E Fernandez MSc), World Health Organization, Geneva, Switzerland; Department of Maternal, Newborn, Child and Adolescent Health and Ageing (A de Costa MD, A C Moran PhD) and Department of Nutrition and Food Safety (G G Domínguez PhD), World Health Organization, Geneva, Switzerland; Division of Data, Analytics, Planning and Monitoring, United Nations Children's Fund, New York, NY, USA (S Chakwera MSc, J Krasevec MSc, J Requejo PhD); Global Health, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (L Hussain-Alkhateeb PhD); Department of Women and Children's Health, Uppsala University, Uppsala, Sweden (E W Johansson PhD)

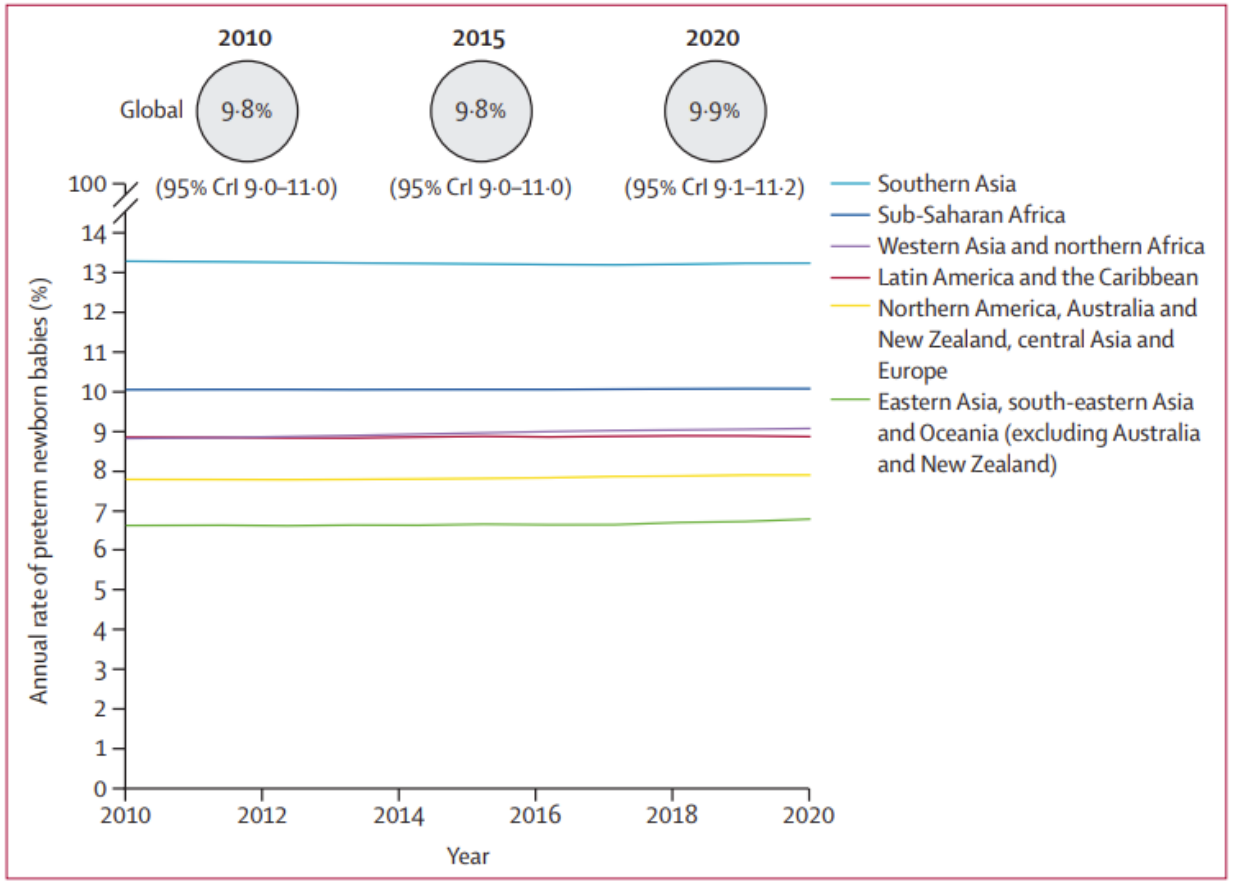


Figure 3: **Regional and worldwide trends in preterm birth between 2010 and 2020**
CrI=credible interval.

Ohuma EO, et al. Lancet. 2023

UT Southwestern Medical Center

Current Rates of Preterm Birth

National Vital Statistics Reports

Volume 73, Number 2 April 4, 2024

Births: Final Data for 2022

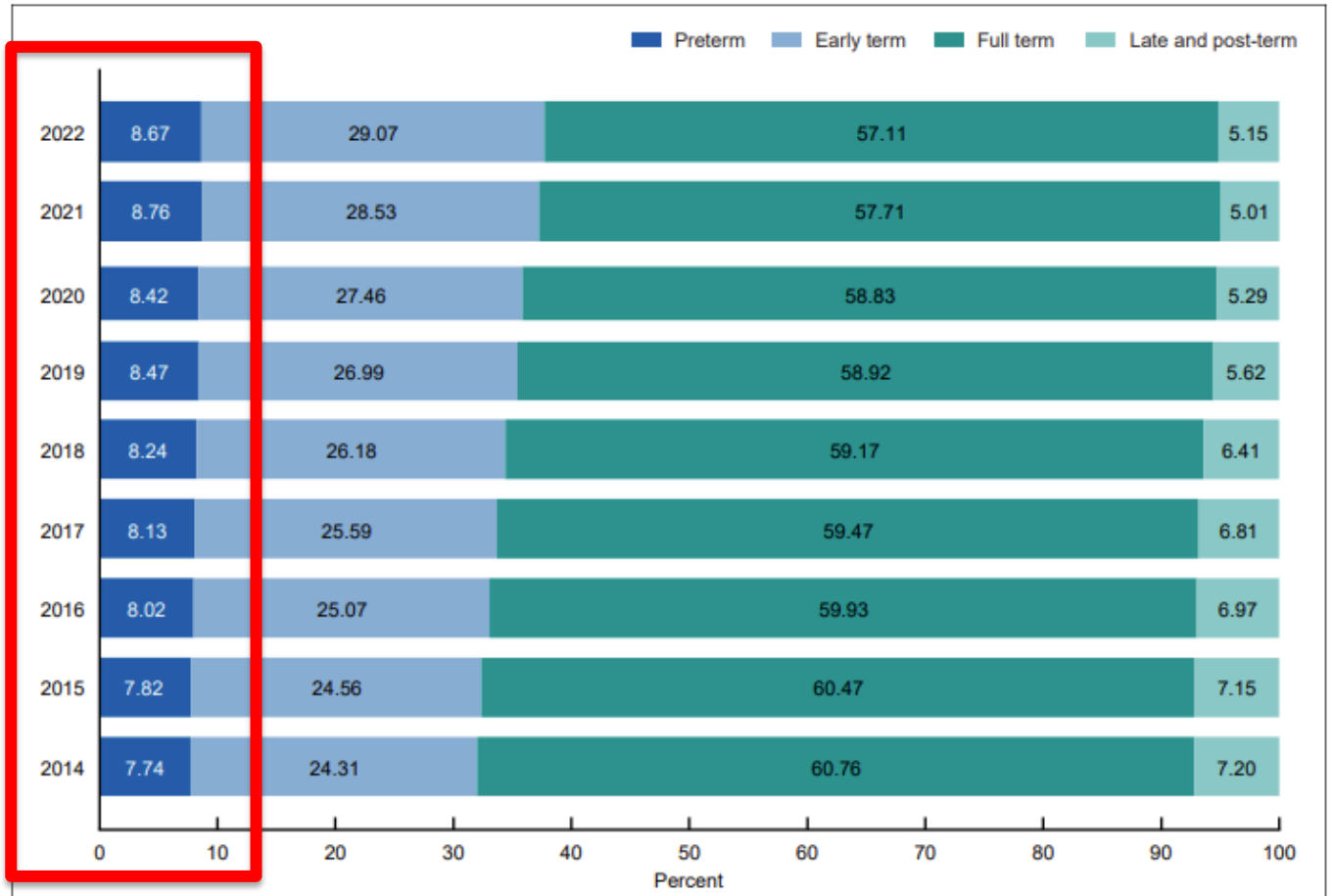
by Michelle J.K. Osterman, M.H.S., Brady E. Hamilton, Ph.D., Joyce A. Martin, M.P.H., Anne K. Driscoll, Ph.D., and Claudia P. Valenzuela, M.P.H.

Abstract

Objectives—This report presents 2022 data on U.S. births by selected characteristics. Trends in fertility patterns and maternal and infant characteristics are described.

Methods—Descriptive tabulations based on birth certificates of the 3.67 million births registered in 2022 are shown by maternal age, live-birth order, race and Hispanic origin, marital status, tobacco use, prenatal care, source of payment for the delivery, method of delivery, gestational age, birthweight, and plurality. Selected data by mother's state of residence and birth rates also are shown. Trends for 2010 to 2022 are presented for selected items, and by race and Hispanic origin for 2016–2022.

Figure 1. Percent distribution of singleton births, by gestational age: United States, 2014–2022



NOTES: Significant changes for all gestational age categories and years ($p < 0.05$). Singleton births only. Preterm is less than 37 weeks of gestation, early term is 37–38 weeks, full term is 39–40 weeks, and late and post-term is 41 weeks and later. Totals may not add to 100 because of rounding.
SOURCE: National Center for Health Statistics, National Vital Statistics System, natality data file.

Osterman MJK, Hamilton BE, Martin JA, Driscoll AK, Valenzuela CP. Births: Final data for 2022. National Vital Statistics Reports; vol 73, no 2. Hyattsville, MD: National Center for Health Statistics. 2024

United States: Infant Mortality, 2021

Total	19,928
Age at death	
Total neonatal	12,797
Early neonatal (under 7 days)	10,082
Late neonatal (7–27 days)	2,715
Postneonatal	7,131
Sex	
Male	10,930
Female	8,998
Period of gestation (weeks)	
Less than 34	10,618
Less than 28	8,323
28–31	1,429
32–33	866
34–36	2,278
37–41	6,812
37–38	3,310
39–40	3,248
41	254
42 or more	34
Not stated	186

In 2021, **65%** of infant deaths occurred among infants born preterm (less than 37 weeks of gestation).

Ely DM, Driscoll AK. Infant mortality in the United States, 2021: Data from the period linked birth/infant death file. National Vital Statistics Reports; vol 72 no 11. Hyattsville, MD: National Center for Health Statistics. 2023

United States: Infant Mortality, 2021

Total	19,928
Age at death	
Total neonatal	12,797
Early neonatal (under 7 days)	10,082
Late neonatal (7–27 days)	2,715
Postneonatal	7,131
Sex	
Male	10,930
Female	8,998
Period of gestation (weeks)	
Less than 34	10,618
Less than 28	8,323
28–31	1,429
32–33	866
34–36	2,278
37–41	6,812
37–38	3,310
39–40	3,248
41	254
42 or more	34
Not stated	186

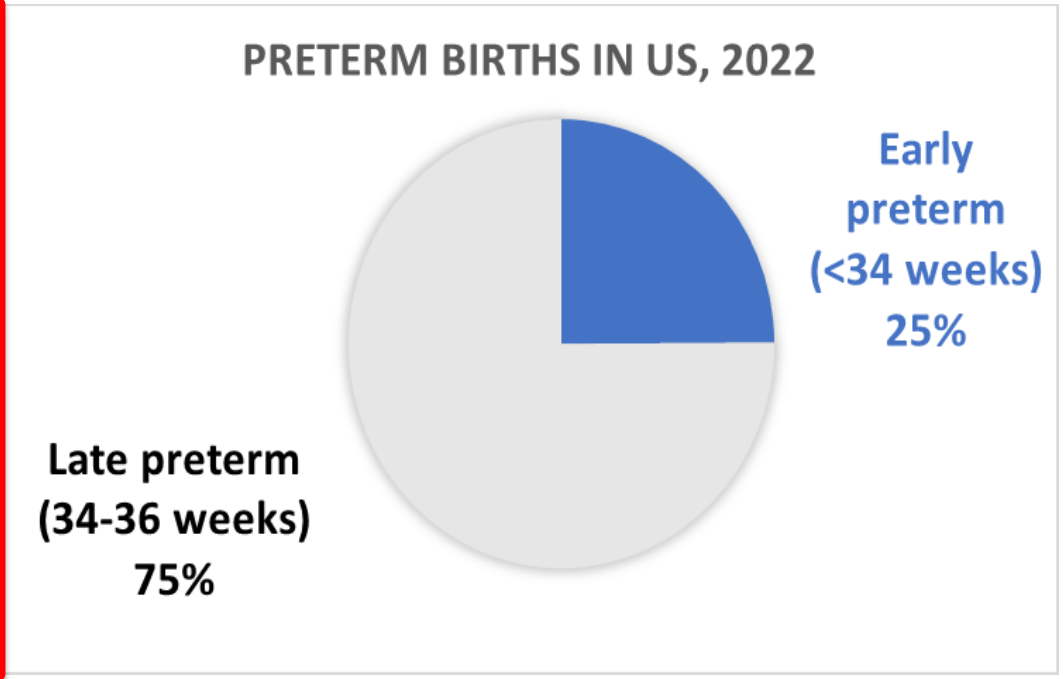
Infant morality rate at less than 28 weeks was ***170 times higher*** than that at 37-41 weeks!

Ely DM, Driscoll AK. Infant mortality in the United States, 2021: Data from the period linked birth/infant death file. National Vital Statistics Reports; vol 72 no 11. Hyattsville, MD: National Center for Health Statistics. 2023

Current Rates of Preterm Birth: United States

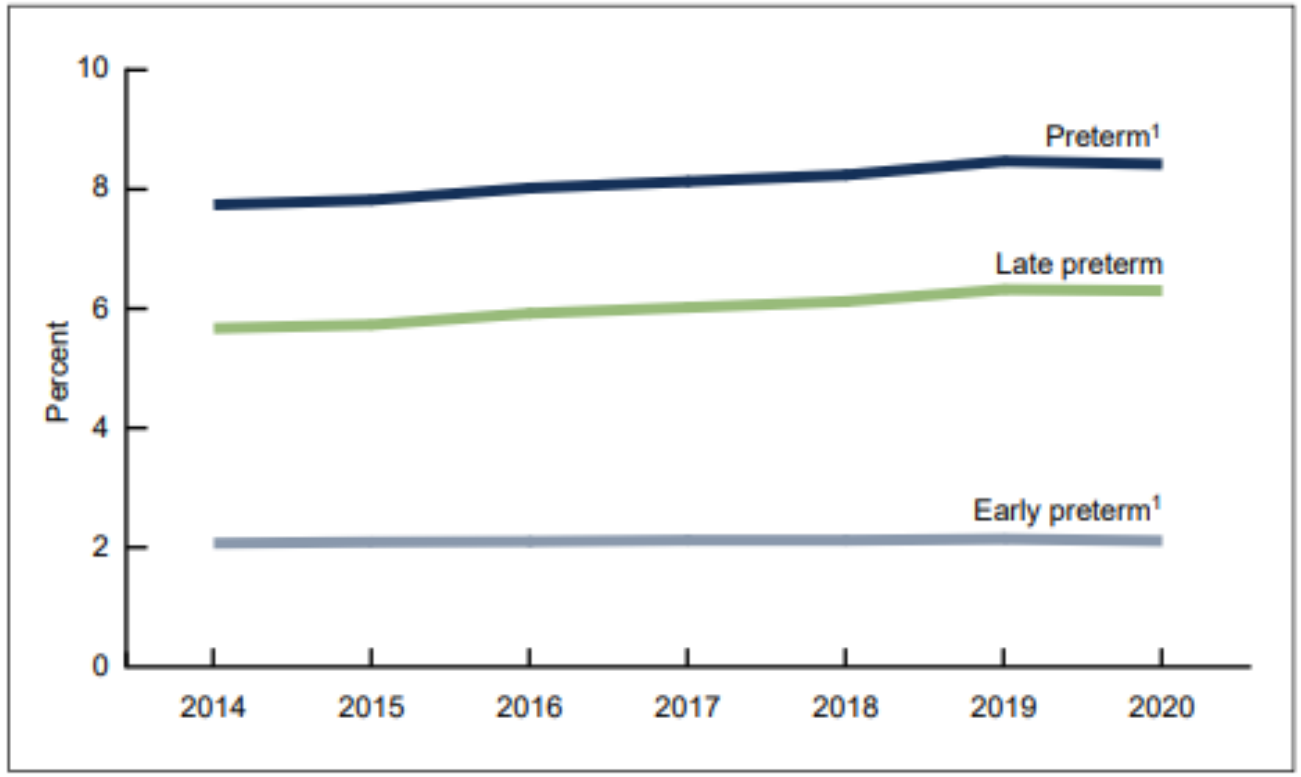
Table 1. Number and percentage of singleton births, by gestational age and race and Hispanic origin of mother: United States, 2014–2022

Race and Hispanic origin and year	All births[1] (number)	Preterm		
		Total (less than 37 weeks)	Early (less than 34 weeks)	Late (34–36 weeks)
All races and origins				Per
2022	3,547,741	8.67	2.16	6.51
2021	3,544,292	8.76	2.20	6.56
2020	3,495,915	8.42	2.11	6.30
2019	3,621,616	8.47	2.14	6.32
2018	3,662,203	8.24	2.12	6.12
2017	3,720,586	8.13	2.12	6.02
2016	3,806,807	8.02	2.10	5.92
2015	3,838,382	7.82	2.09	5.73
2014	3,845,046	7.74	2.07	5.67



Martin JA, Osterman MJK. Shifts in the distribution of births by gestational age: United States, 2014–2022. National Vital Statistics Reports; vol 73 no 1. Hyattsville, MD: National Center for Health Statistics. 2024

Singleton preterm birth rates: United States, 2014–2020

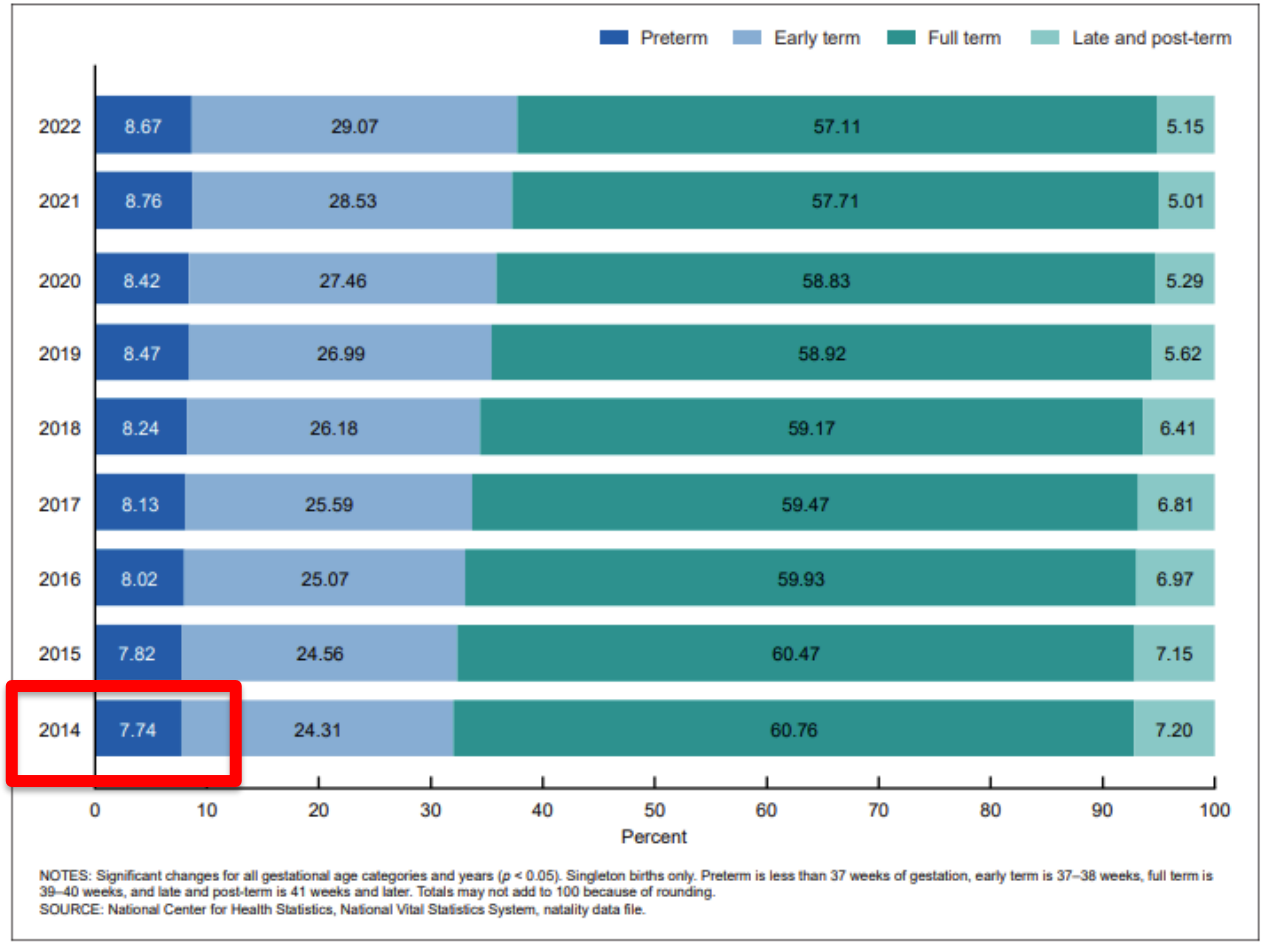


[1]Significant decline between 2019 and 2020 ($p < 0.05$).
NOTES: Generally increasing significant trend from 2014 to 2019 ($p < 0.05$). Preterm is births at less than 37 completed weeks of gestation, late preterm is births at 34–36 weeks, and early preterm is births at less than 34 weeks. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db430-tables.pdf#1.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

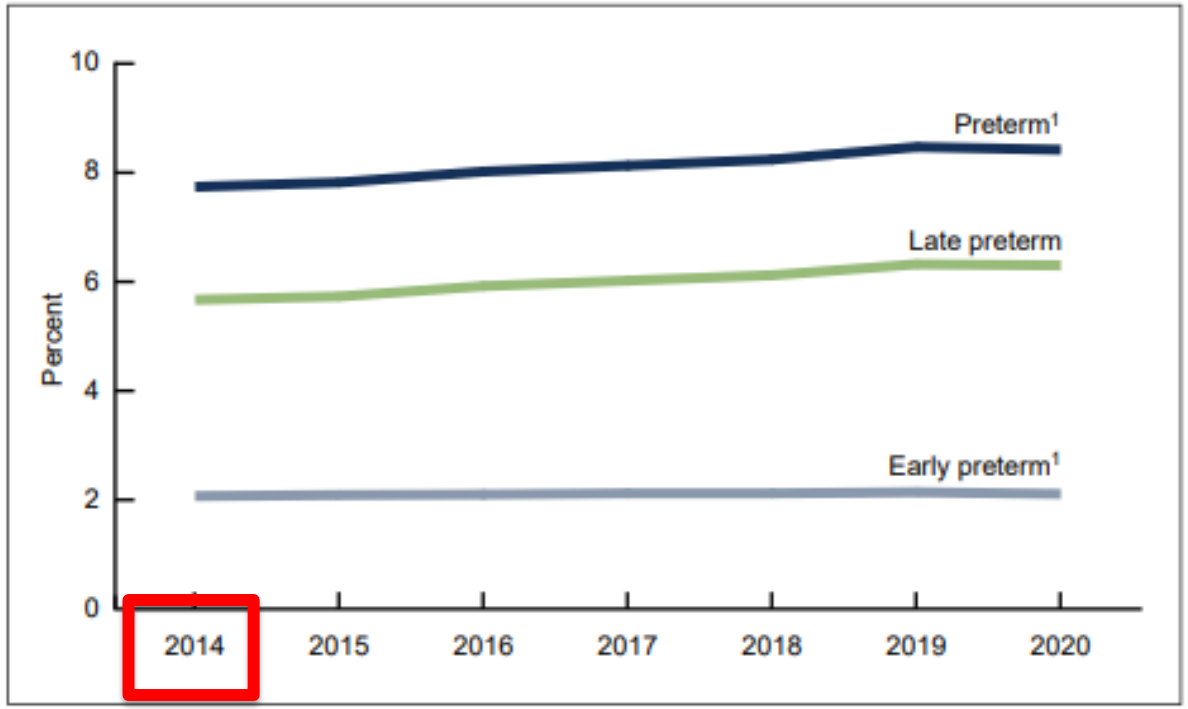
Martin JA, Osterman MJK. Exploring the decline in the singleton preterm birth rate in the United States, 2019–2022. NCHS Data Brief, no 430. Hyattsville, MD: National Center for Health Statistics. 2022.

Current Rates of Preterm Birth: United States

Figure 1. Percent distribution of singleton births, by gestational age: United States, 2014–2022



NOTES: Significant changes for all gestational age categories and years ($p < 0.05$). Singleton births only. Preterm is less than 37 weeks of gestation, early term is 37–38 weeks, full term is 39–40 weeks, and late and post-term is 41 weeks and later. Totals may not add to 100 because of rounding.
SOURCE: National Center for Health Statistics, National Vital Statistics System, natality data file.



[1]Significant decline between 2019 and 2020 ($p < 0.05$).
NOTES: Generally increasing significant trend from 2014 to 2019 ($p < 0.05$). Preterm is births at less than 37 completed weeks of gestation, late preterm is births at 34–36 weeks, and early preterm is births at less than 34 weeks. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db430-tables.pdf#1.
SOURCE: National Center for Health Statistics, National Vital Statistics System, Natality.

Current Rates of Preterm Birth: Caution with unit of measure

National Vital Statistics Reports

Volume 64, Number 5 June 1, 2015

Measuring Gestational Age in Vital Statistics Data: Transitioning to the Obstetric Estimate

Joyce A. Martin, M.P.H.; Michelle J.K. Osterman, M.H.S.; Sharon E. Kirmeyer, Ph.D.; and Elizabeth C.W. Gregory, M.P.H., Division of Vital Statistics

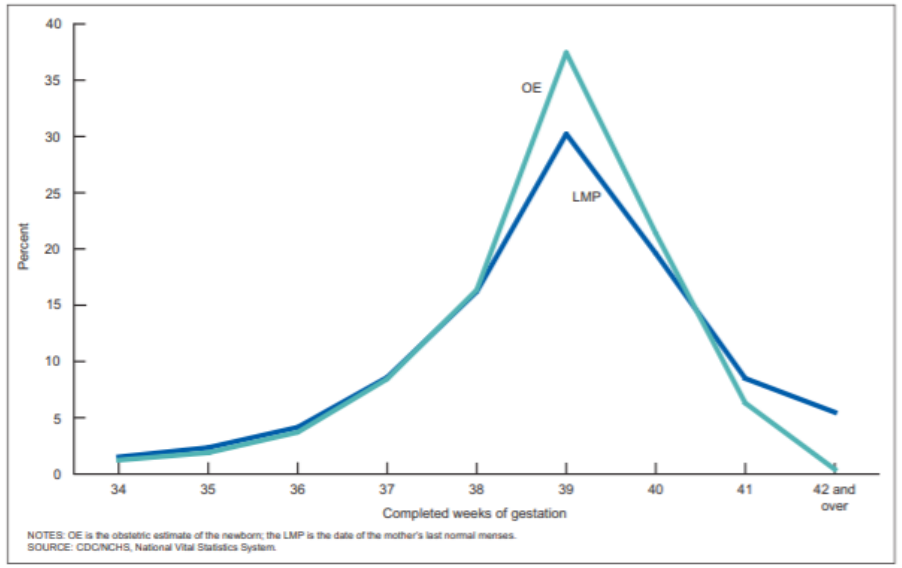


Figure 1. OE- and LMP-based measures of gestational age for selected weeks: United States, 2013

Gestational age

Beginning with the 2014 data year, NCHS transitioned to a new standard for estimating the gestational age of the newborn. The new measure–the obstetric estimate of gestation at delivery (OE)–replaces the measure based on the date of the last normal menses (LMP) (20). National data based on the OE are available only from data year 2007 forward. Gestational age estimates differ somewhat between the OE- and LMP-based measures. Accordingly, gestational age data in this report are based on the OE. Information and discussion of the reasons for the change, and a detailed comparison of the two measures, are presented elsewhere (20).

Martin JA, Osterman MJK, Kirmeyer SE, Gregory ECW. Measuring gestational age in vital statistics data: Transitioning to the obstetric estimate. National vital statistics reports; vol 64 no 5. Hyattsville, MD: National Center for Health Statistics. 2015

Current Rates of Preterm Birth: Caution with unit of measure

National Vital Statistics Reports

Volume 64, Number 5 June 1, 2015

Measuring Gestational Age in Vital Statistics Data: Transitioning to the Obstetric Estimate

Joyce A. Martin, M.P.H.; Michelle J.K. Osterman, M.H.S.; Sharon E. Kirmeyer, Ph.D.; and Elizabeth C.W. Gregory, M.P.H., Division of Vital Statistics

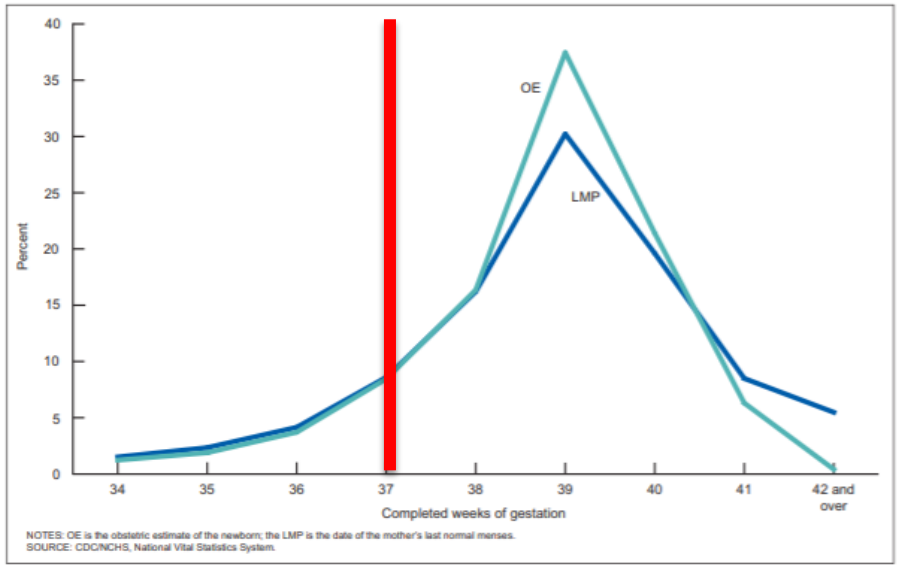


Figure 1. OE- and LMP-based measures of gestational age for selected weeks: United States, 2013

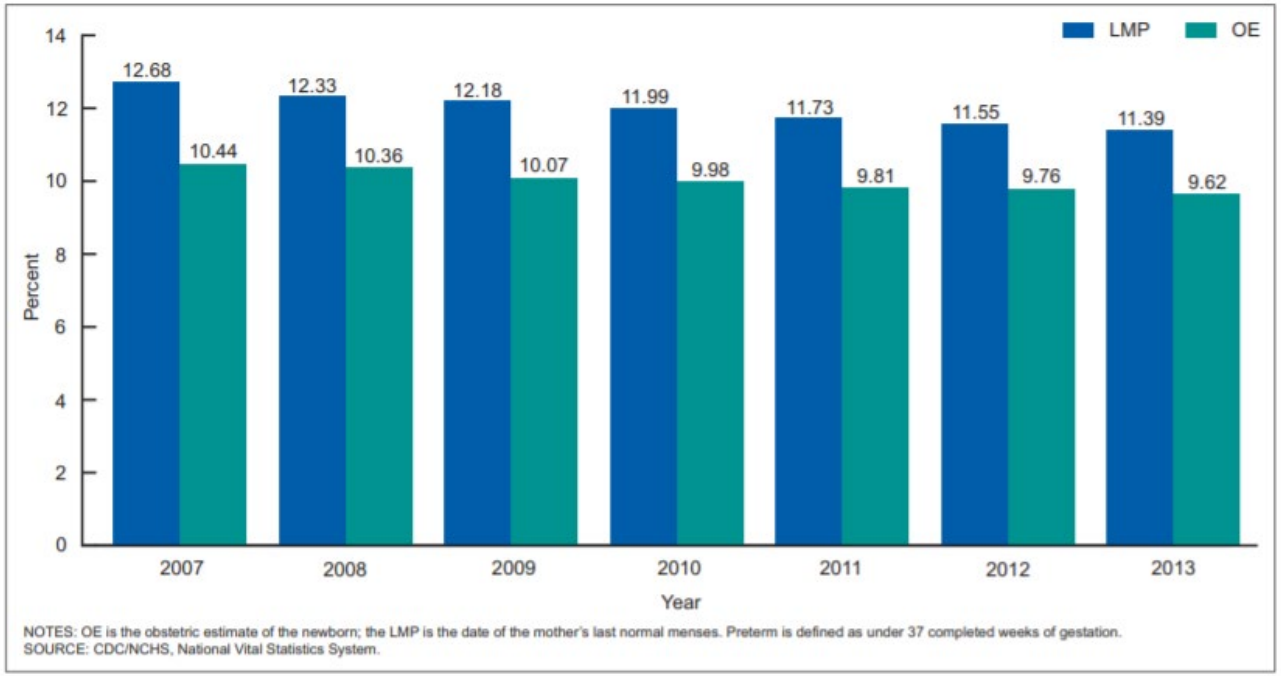


Figure 2. Preterm births, by OE- and LMP-based measures of gestational age: United States, 2007–2013

Martin JA, Osterman MJK, Kirmeyer SE, Gregory ECW. Measuring gestational age in vital statistics data: Transitioning to the obstetric estimate. National vital statistics reports; vol 64 no 5. Hyattsville, MD: National Center for Health Statistics. 2015

Current Rates of Preterm Birth: Caution with unit of measure

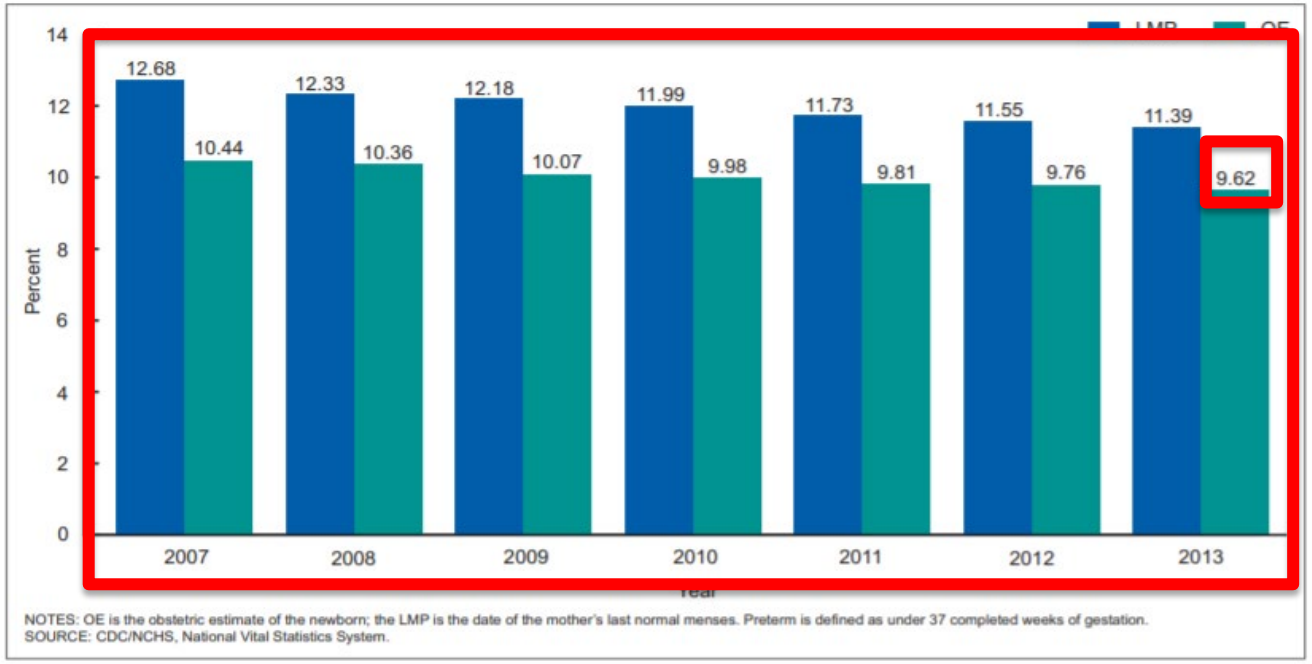
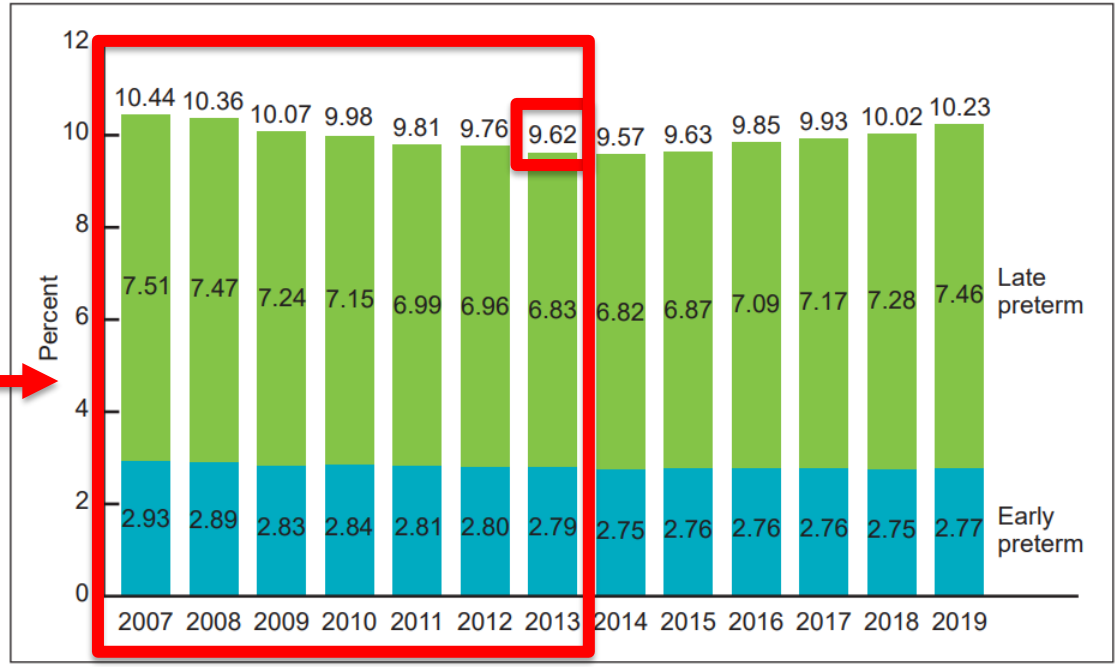


Figure 2. Preterm births, by OE- and LMP-based measures of gestational age: United States, 2007–2013



NOTES: Gestational age is based on the obstetric estimate of gestation. Preterm is less than 37 completed weeks, late preterm is 34–36 completed weeks, and early preterm is less than 34 completed weeks of gestation.
SOURCE: NCHS, National Vital Statistics System, Natality.

Martin JA, Osterman MJK, Kirmeyer SE, Gregory ECW. Measuring gestational age in vital statistics data: Transitioning to the obstetric estimate. National vital statistics reports; vol 64 no 5. Hyattsville, MD: National Center for Health Statistics. 2015

Hamilton BE, Martin JA, Osterman MJK. Births: Provisional data for 2019. Vital Statistics Rapid Release; no 8. Hyattsville, MD: National Center for Health Statistics. May 2020.

Healthcare costs from preterm birth, 2005

*"…the annual societal economic burden associated with preterm birth in the United States was at least **$26.2 billion** in 2005, or $51,600 per infant born preterm."*

Institute of Medicine. 2007

Healthcare costs from preterm birth, 2019

Table 2. National Total and Per Capita Cost of Preterm Birth by Category of Cost, 2016

Category of Cost	Total ($)	Per Preterm Birth ($)
Medical Care for Affected Child	17,126,625,946	44,116
Maternal Delivery Costs	1,950,230,570	5,024
Early Intervention Services (EI)	702,014,493	1,808
Special Education Services	622,589,060	1,604
Devices	10,820,563	28
Lost Labor Market Productivity	4,750,215,975	12,236
Total	25,162,496,608	64,815

Waitzman NJ, et al. March of Dimes. 2019

Healthcare costs from preterm birth

- Had price changes been the sole source of change since the societal cost estimates in the IOM report, the total national cost of preterm birth would be **$32 billion**, $6.8 billion higher than the $25.2 billion reported, an increase of $5.8 billion, or 22%, over the earlier estimate.

- Other factors affecting costs changed in a way to generate a net decrease in total cost of $1 billion relative to the previous estimate of $26.2 billion in 2005 dollars.

- ***The major one was the change in 2014 in the official method for assessing GA from the last normal menses (LMP) to the obstetric estimate (OE).*** This resulted in a significant reduction in the rate of preterm birth.

Waitzman NJ, et al. March of Dimes. 2019

Later-life morbidity

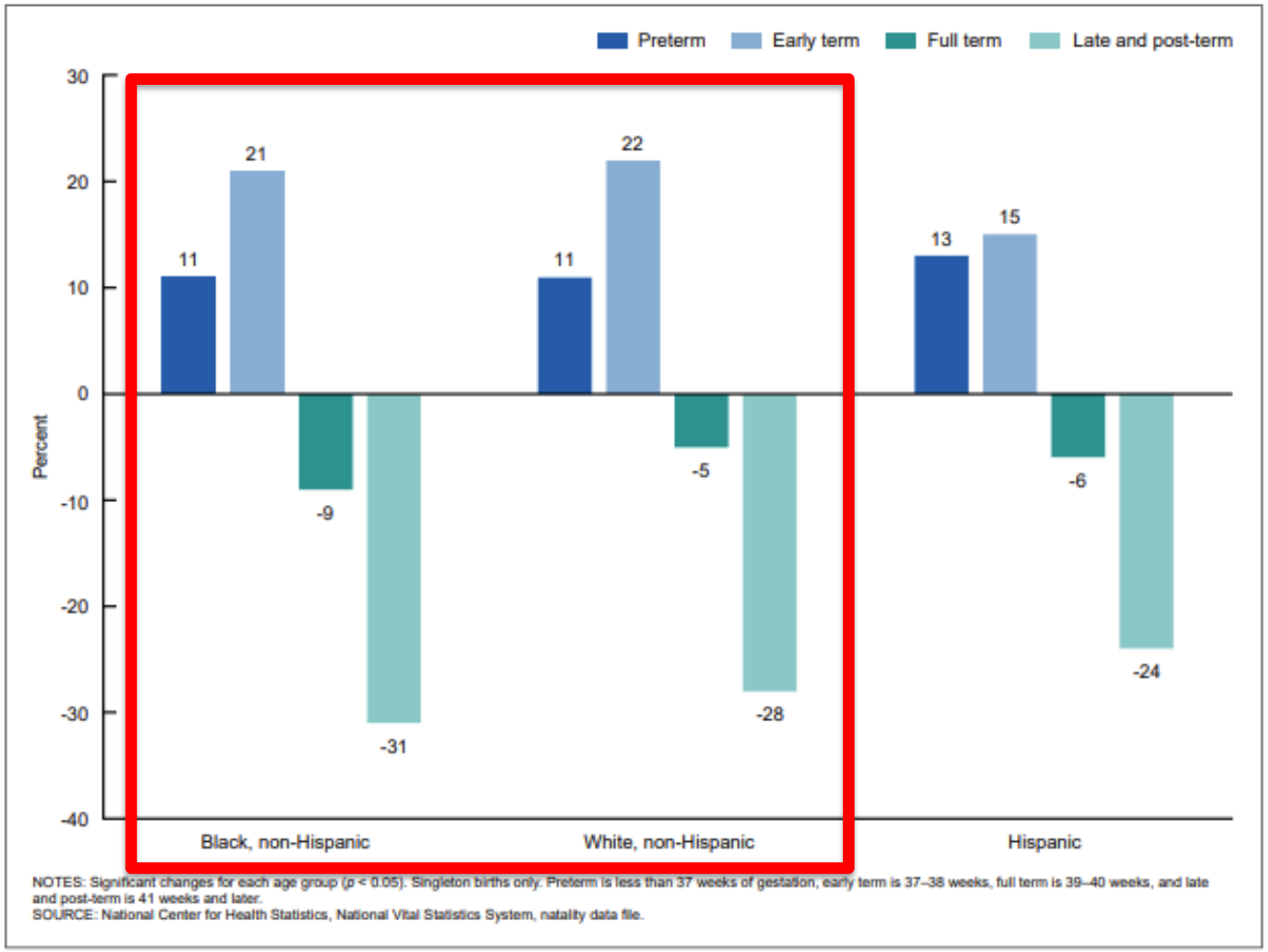
Table 1. Major Short- and Long-Term Problems in Very-Low-Birth-Weight Infants.

Affected Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity	Bronchopulmonary dysplasia, reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure	Failure to thrive, short-bowel syndrome, cholestasis
Immunologic	Hospital-acquired infection, immune deficiency, perinatal infection	Respiratory syncytial virus infection, bronchiolitis
Central nervous system	Intraventricular hemorrhage, periventricular white-matter injury, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss
Ophthalmologic	Retinopathy of prematurity	Blindness, retinal detachment, myopia, strabismus
Cardiovascular	Hypotension, patent ductus arteriosus, pulmonary hypertension	Pulmonary hypertension, hypertension in adulthood
Renal	Water and electrolyte imbalance, acid–base disturbances	Hypertension in adulthood
Hematologic	Iatrogenic anemia, need for frequent transfusions, anemia of prematurity	
Endocrine	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

Eichenwald EC, Stark AR. N Engl J Med. 2008

Current Rates of Preterm Birth: United States

Figure 3. Percent change in gestational age category, by race and Hispanic origin of mother: United States, 2014 and 2022



NOTES: Significant changes for each age group ($p < 0.05$). Singleton births only. Preterm is less than 37 weeks of gestation, early term is 37–38 weeks, full term is 39–40 weeks, and late and post-term is 41 weeks and later.
SOURCE: National Center for Health Statistics, National Vital Statistics System, natality data file.

Martin JA, Osterman MJK. Shifts in the distribution of births by gestational age: United States, 2014–2022. National Vital Statistics Reports; vol 73 no 1. Hyattsville, MD: National Center for Health Statistics. 2024

Burden of preterm birth

1. Substantial issue worldwide with rates essentially unchanged for the past decade.

2. Late preterm birth represents the majority of events, but morbidity and mortality significantly increase for early preterm births.

3. Methodology for aggregate calculations are complex (beware with comparisons from prior years).

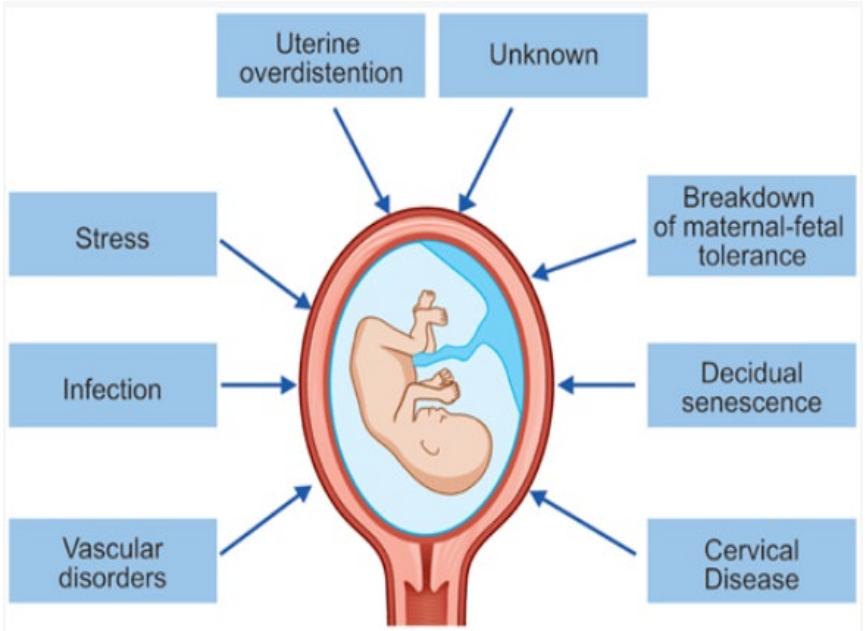
4. Significant health disparity for pregnant individuals.

Use of progestogens in preterm birth prevention

Risk factors for preterm birth

- Vaginal Bleeding
- Lifestyle factors
- Work During Pregnancy
- Genetics
- Periodontal Disease
- Birth Defects
- Intervals Between Pregnancy
- Prior Preterm Birth
- Cervical factors

Complex poorly understood mechanism for spontaneous preterm birth



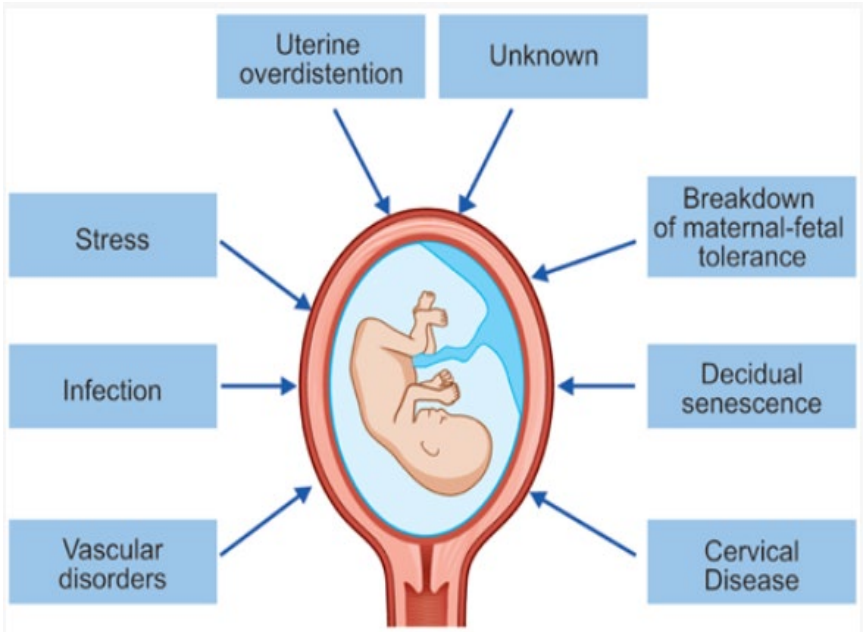
- History of cervical surgery
- Placental factors (previa, abruption)
- Multiple Gestations
- Fetal factors (anomalies, growth restriction)
- Uterine Anomaly
- Polyhydramnios
- Inadequate prenatal care
- Infection

Williams Obstetrics. 26th ed.

Risk factors for preterm birth

- Vaginal Bleeding
- Lifestyle factors
- Work During Pregnancy
- Genetics
- Periodontal Disease
- Birth Defects
- Intervals Between Pregnancy
- **Prior Preterm Birth**
- Cervical factors

Complex poorly understood mechanism for spontaneous preterm birth



- History of cervical surgery
- Placental factors (previa, abruption)
- Multiple Gestations
- Fetal factors (anomalies, growth restriction)
- Uterine Anomaly
- Polyhydramnios
- Inadequate prenatal care
- Infection

Williams Obstetrics. 26th ed.

Prior Preterm Birth

Recurrence of Preterm Birth in Singleton and Twin Pregnancies

Steven L. Bloom, MD, Nicole P. Yost, MD, Donald D. McIntire, PhD, and Kenneth J. Leveno, MD

OBJECTIVE: To assess recurrence of preterm birth and its impact on an obstetric population.

METHODS: Women with consecutive births at our hospital beginning with their first pregnancy were identified (n = 15,945). The first pregnancy was categorized as delivered between 24 and 34 weeks' gestation or 35 weeks or beyond, singleton or twin, and spontaneous or induced. The risk of preterm delivery in these same women during subsequent pregnancies was then analyzed.

RESULTS: Compared with women who delivered a singleton at or beyond 35 weeks' gestation in their first pregnancy, those who delivered a singleton before 35 weeks were at a significant increased risk for recurrence (odds ratio [OR] 5.6, 95% confidence interval [CI] 4.5, 7.0), whereas those who delivered twins were not (OR 1.9, 95% CI 0.46, 8.14). The OR for recurrent spontaneous preterm birth presenting with intact membranes was 7.9 (95% CI 5.6, 11.3) compared with 5.5 (95% CI 3.2, 9.4) with ruptured membranes. Of those women with a recurrent preterm birth, 49% delivered within 1 week of the gestational age of their first delivery and 70% delivered within 2 weeks. Among 15,863 nulliparous women with singleton births at their first delivery, a history of preterm birth in that pregnancy could predict only 10% of the preterm births that ultimately occurred in the entire obstetric population.

CONCLUSION: In a population-based study at our hospital, women who initially delivered preterm and thus were identified to be at risk for recurrence ultimately accounted for only 10% of the prematurity problem in the cohort. (Obstet Gynecol 2001;98:379–85. © 2001 by the American College of Obstetricians and Gynecologists.)

A history of a prior preterm birth is generally accepted to be a significant risk factor for recurrence in a future pregnancy. With the recent advent of tests designed to improve the identification of women at risk for preterm delivery, the risk associated with history alone may become inappropriately minimized. In a recent multicenter investigation, for example, the odds ratios (OR) for preterm birth less than 35 weeks' gestation associated with markers of preterm delivery such as detection of fetal fibronectin in cervical secretions (OR 5.2), ultrasonic shortening of the cervix (OR 4.1), and colonization of the genital tract with bacterial vaginosis (OR 1.3) were all lower than the risk of recurrence based solely upon a history of prior preterm birth (OR 5.8).[1]

Although a general, nonspecific history of preterm birth is accepted to be a risk factor for recurrence, there is little information on the recurrence risk for specific types of prior preterm deliveries.[2] Moreover, given the recent increase in twin gestations,[3] it is unclear if spontaneous preterm delivery of twins modifies a woman's risk for a subsequent preterm birth. Stated differently, does a history of a spontaneous preterm twin delivery convey the same risk for recurrence as does a history of a spontaneous preterm singleton delivery? Lastly, what is the contribution of women with recurrent preterm delivery to the overall problem of prematurity in an obstetric population?

Since 1988, we have collected information on pregnancy outcomes for all women delivering at our institution. With over 10 years of computerized data involving nearly 170,000 women, many of whom with more than one delivery at our hospital, we had the opportunity to analyze the reproductive histories of a cohort of over 15,000 women beginning with their first delivery and including all subsequent consecutive pregnancies. The purpose of this analysis was to measure the risk of recurrent preterm birth based on 1) whether the first delivery was a preterm singleton or twin, 2) the labor was spontaneous or induced, 3) the timing of recurrence, and 4) the overall contribution these women made to preterm births in the study cohort.

MATERIALS AND METHODS

Women with consecutive pregnancies, beginning with their first birth, and who were delivered at our hospital between January 1, 1988, and December 31, 1999, were identified using a computerized database. This database

From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas.

VOL. 98, NO. 3, SEPTEMBER 2001

0029-7844/01/$20.00 PII S0029-7844(01)01466-1

1st birth ≤ 34 weeks→ **16%** risk next birth ≤ 34 weeks

1st and 2nd births ≤ 34 weeks→ **41%** risk next birth ≤ 34 weeks

1st , 2nd , and 3rd births ≤ 34 weeks→ **67%** risk next birth ≤ 34 weeks

Bloom et al. Obstet Gynecol. 2001

Prior Preterm Birth

Recurrence of Preterm Birth in Singleton and Twin Pregnancies

Steven L. Bloom, MD, Nicole P. Yost, MD, Donald D. McIntire, PhD, and Kenneth J. Leveno, MD

OBJECTIVE: To assess recurrence of preterm birth and its impact on an obstetric population.

METHODS: Women with consecutive births at our hospital beginning with their first pregnancy were identified (n = 15,945). The first pregnancy was categorized as delivered between 24 and 34 weeks' gestation or 35 weeks or beyond, singleton or twin, and spontaneous or induced. The risk of preterm delivery in these same women during subsequent pregnancies was then analyzed.

RESULTS: Compared with women who delivered a singleton at or beyond 35 weeks' gestation in their first pregnancy, those who delivered a singleton before 35 weeks were at a significant increased risk for recurrence (odds ratio [OR] 5.6, 95% confidence interval [CI] 4.5, 7.0), whereas those who delivered twins were not (OR 1.9, 95% CI 0.46, 8.14). The OR for recurrent spontaneous preterm birth presenting with intact membranes was 7.9 (95% CI 5.6, 11.3) compared with 5.5 (95% CI 3.2, 9.4) with ruptured membranes. Of those women with a recurrent preterm birth, 49% delivered within 1 week of the gestational age of their first delivery and 70% delivered within 2 weeks. Among 15,863 nulliparous women with singleton births at their first delivery, a history of preterm birth in that pregnancy could predict only 10% of the preterm births that ultimately occurred in the entire obstetric population.

CONCLUSION: In a population-based study at our hospital, women who initially delivered preterm and thus were identified to be at risk for recurrence ultimately accounted for only 10% of the prematurity problem in the cohort. (Obstet Gynecol 2001;98:379–85. © 2001 by the American College of Obstetricians and Gynecologists.)

A history of a prior preterm birth is generally accepted to be a significant risk factor for recurrence in a future pregnancy. With the recent advent of tests designed to improve the identification of women at risk for preterm delivery, the risk associated with history alone may become inappropriately minimized. In a recent multicenter investigation, for example, the odds ratios (OR) for preterm birth less than 35 weeks' gestation associated with markers of preterm delivery such as detection of fetal fibronectin in cervical secretions (OR 5.2), ultrasonic shortening of the cervix (OR 4.1), and colonization of the genital tract with bacterial vaginosis (OR 1.3) were all lower than the risk of recurrence based solely upon a history of prior preterm birth (OR 5.8).[1]

Although a general, nonspecific history of preterm birth is accepted to be a risk factor for recurrence, there is little information on the recurrence risk for specific types of prior preterm deliveries.[2] Moreover, given the recent increase in twin gestations,[3] it is unclear if spontaneous preterm delivery of twins modifies a woman's risk for a subsequent preterm birth. Stated differently, does a history of a spontaneous preterm twin delivery convey the same risk for recurrence as does a history of a spontaneous preterm singleton delivery? Lastly, what is the contribution of women with recurrent preterm delivery to the overall problem of prematurity in an obstetric population?

Since 1988, we have collected information on pregnancy outcomes for all women delivering at our institution. With over 10 years of computerized data involving nearly 170,000 women, many of whom with more than one delivery at our hospital, we had the opportunity to analyze the reproductive histories of a cohort of over 15,000 women beginning with their first delivery and including all subsequent consecutive pregnancies. The purpose of this analysis was to measure the risk of recurrent preterm birth based on 1) whether the first delivery was a preterm singleton or twin, 2) the labor was spontaneous or induced, 3) the timing of recurrence, and 4) the overall contribution these women made to preterm births in the study cohort.

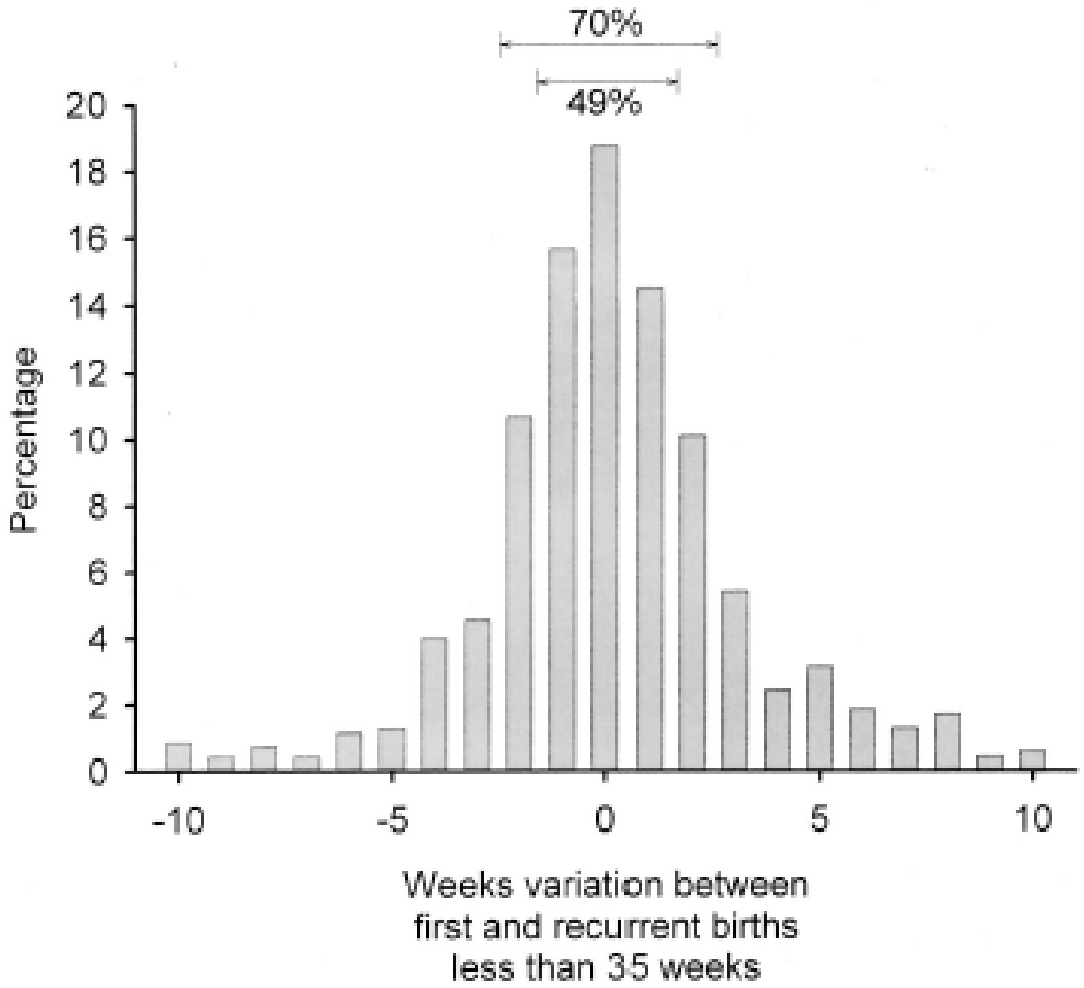
MATERIALS AND METHODS

Women with consecutive pregnancies, beginning with their first birth, and who were delivered at our hospital between January 1, 1988, and December 31, 1999, were identified using a computerized database. This database

From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas.

VOL. 98, NO. 3, SEPTEMBER 2001

0029-7844/01/$20.00 PII S0029-7844(01)01466-1



Bloom et al. Obstet Gynecol. 2001

UTSouthwestern Medical Center

Role of progesterone in pregnancy

- Early in pregnancy: support of the pregnancy
- Later in pregnancy: ???
- Progesterone levels in most mammals fall rapidly before the onset of labor—that is, “progesterone withdrawal”
- Human parturition, not so simple…

Csapo "See Saw Theory"

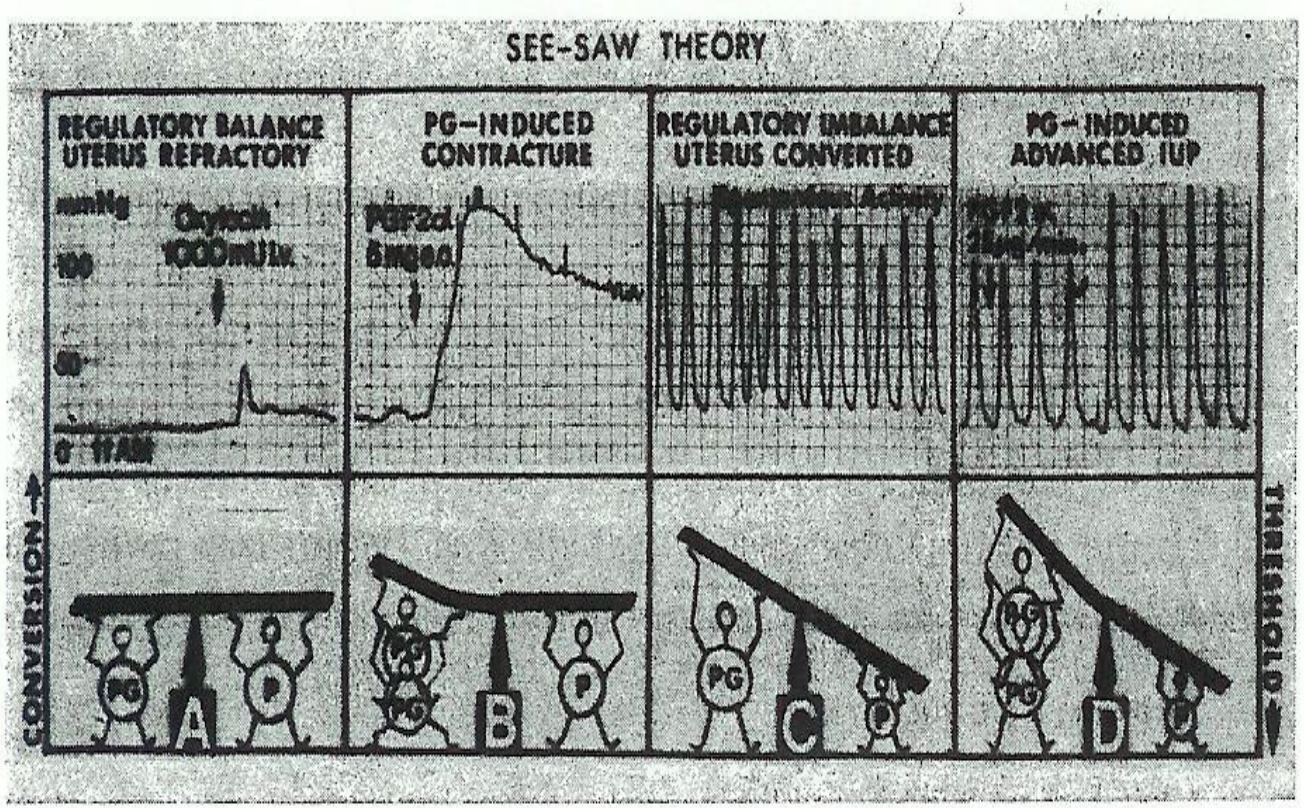
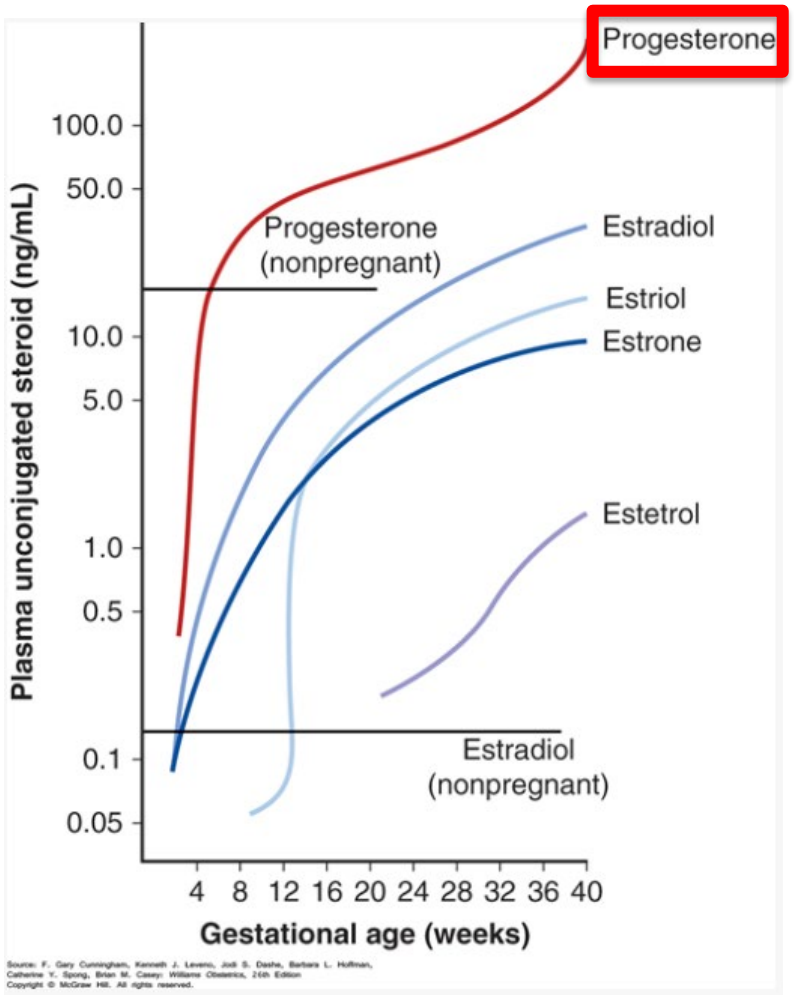


FIG. 1. The four basic positions of the see-saw, reflecting four regulatory conditions of the pregnant uterus.

Csapo. Ciba Found Symp. 1977

“Functional” progesterone withdrawal



Williams Obstetrics. 26th ed.

Acta Obstetricia et Gynecologica. 2010; 89: 705–711

informa healthcare

MAIN RESEARCH ARTICLE

Regulation of progesterone receptor A and B expression in human preterm, term, and postterm placental villi

JIANG ZIYAN[1], REN HUAIBIN[1], MA XIAOTIAN[1], SHE GUANGTONG[1], CHEN XIAOQING[1], DONG ZIJIANG[1], JIANG ZIYUE[4], DE WE[2] & SUN LIZHOU[1,3]

[1]*Department of Obstetrics and Gynaecology, Nanjing Medical University, Nanjing, China,* [2]*Department of Biochemistry, Nanjing Medical University, Nanjing, China,* [3]*Department of Obstetrics and Gynaecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, and* [4]*Department of Chemistry, Nanjing Xiaozhuang University, Nanjing, China*

Abstract

Objective. The progesterone receptor (PR)-A/B ratio in the myometrium is reported to be closely related to labor onset. This might represent a potential target for therapeutic interventions for postterm and preterm deliveries, though the mechanisms currently remain unknown. The aim of this study was to investigate the regulation mechanism of PR-A and B expression in human preterm, term, and postterm placental villi. *Design.* Experimental study. *Setting.* People's Hospital of Jiangsu Province, China. *Population.* Singleton women of preterm (PRNIL, not in labor, $n = 10$), term (TNIL, not in labor, $n = 10$; TIL, in labor, $n = 10$), and postterm (PONIL, not in labor, $n = 10$) cesarean deliveries. *Methods.* The PR-A/PR-B mRNA and protein ratios were analyzed using real-time reverse transcription-polymerase chain reaction and western blots in villi from preterm, term, postterm groups. PONIL and PRNIL villi were incubated with prostaglandin $F_{2\alpha}$ (PG) and indomethacin for 72 hours, respectively, and the PR-A/PR-B mRNA and protein ratios and p38 signaling pathway were explored. *Results.* The PR-A/PR-B ratio was highest in TIL, followed by PRNIL, PONIL and TNIL. Indomethacin significantly up-regulated PR-B expression, thereby decreasing the PR-A/PR-B ratio ($p < 0.05$). Meanwhile, PG reduced the expression of PR-B and increased PR-A, leading to a significant increase in the PR-A/PR-B ratio ($p < 0.05$). We also determined that the PR-A/PR-B ratio was mediated through the activation of p38 mitogen-activated protein kinase. *Conclusion.* These results demonstrate that the PR-A/PR-B ratio plays a key role in the mechanisms regulating preterm, term, and postterm deliveries.

Key words: *PR-A/PR-B ratio, preterm, postterm, indomethacin, prostaglandin $F_{2\alpha}$*

Introduction

Progesterone levels in most mammals fall rapidly before the onset of labor. This has been called ‘progesterone withdrawal’ and is considered to be a parturition-triggering event (1). During human parturition, however, maternal, fetal and amniotic fluid progesterone levels remain elevated, with no decline (2). It has therefore been proposed that human parturition involves functional progesterone withdrawal mediated by decreased progesterone activity due to alterations in the expression of progesterone receptors (PRs). PRs are divided into two main types: a full-length PR-B and an *N*-terminal-truncated PR-A (3). Structurally, the PR-A protein lacks the last 164 amino acids found at the *N*-terminal end of the PR-B protein. PR-A thus differs from PR-B in lacking the region containing the third transcription activation factor 3 (AF3) (4). It is generally accepted that PR-A acts as a transcription inhibitor of PR-B, which is the main executor responsible for maintaining pregnancy. Previous studies focusing on the relation

Correspondence: Sun Lizhou, Department of Obstetrics and Gynaecology, the First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China. E-mail: lizhou_sun121@hotmail.com

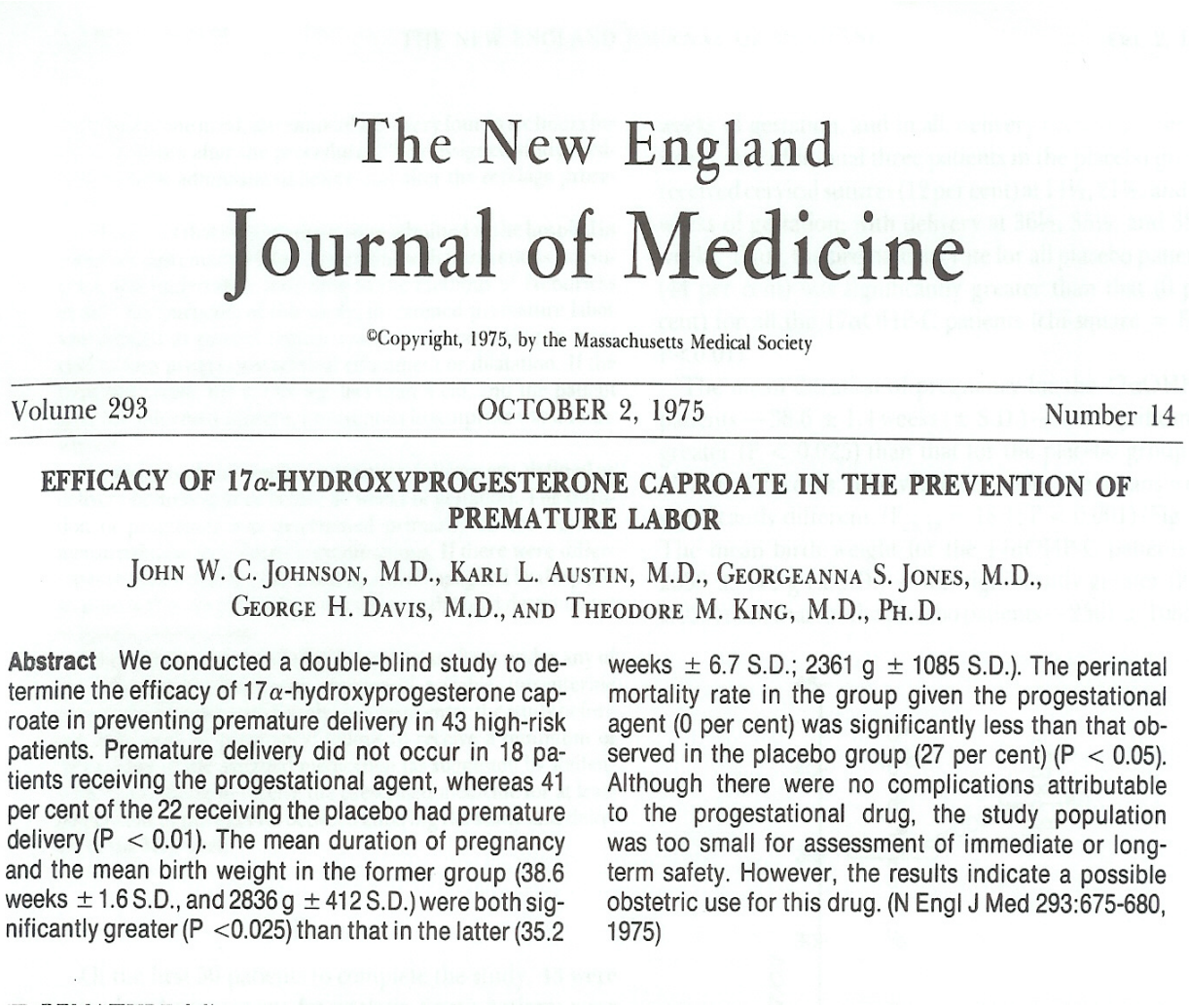
Supported by: The project of six peak talent of Jiangsu Province, Grant NO.DG216D5019

(Received 11 October 2009; accepted 12 January 2010)

ISSN 0001-6349 print/ISSN 1600-0412 online © 2010 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)
DOI: 10.3109/00016341003623761

Ziyan et al. Acta Obstetric Gyn. 2010

Progestogen use in recurrent spontaneous preterm birth prevention



The New England Journal of Medicine

Volume 293 OCTOBER 2, 1975 Number 14

EFFICACY OF 17α-HYDROXYPROGESTERONE CAPROATE IN THE PREVENTION OF PREMATURE LABOR

JOHN W. C. JOHNSON, M.D., KARL L. AUSTIN, M.D., GEORGEANNA S. JONES, M.D., GEORGE H. DAVIS, M.D., AND THEODORE M. KING, M.D., PH.D.

Abstract We conducted a double-blind study to determine the efficacy of 17α-hydroxyprogesterone caproate in preventing premature delivery in 43 high-risk patients. Premature delivery did not occur in 18 patients receiving the progestational agent, whereas 41 per cent of the 22 receiving the placebo had premature delivery ($P < 0.01$). The mean duration of pregnancy and the mean birth weight in the former group (38.6 weeks ± 1.6 S.D., and 2836 g ± 412 S.D.) were both significantly greater ($P < 0.025$) than that in the latter (35.2 weeks ± 6.7 S.D.; 2361 g ± 1085 S.D.). The perinatal mortality rate in the group given the progestational agent (0 per cent) was significantly less than that observed in the placebo group (27 per cent) ($P < 0.05$). Although there were no complications attributable to the progestational drug, the study population was too small for assessment of immediate or long-term safety. However, the results indicate a possible obstetric use for this drug. (N Engl J Med 293:675-680, 1975)

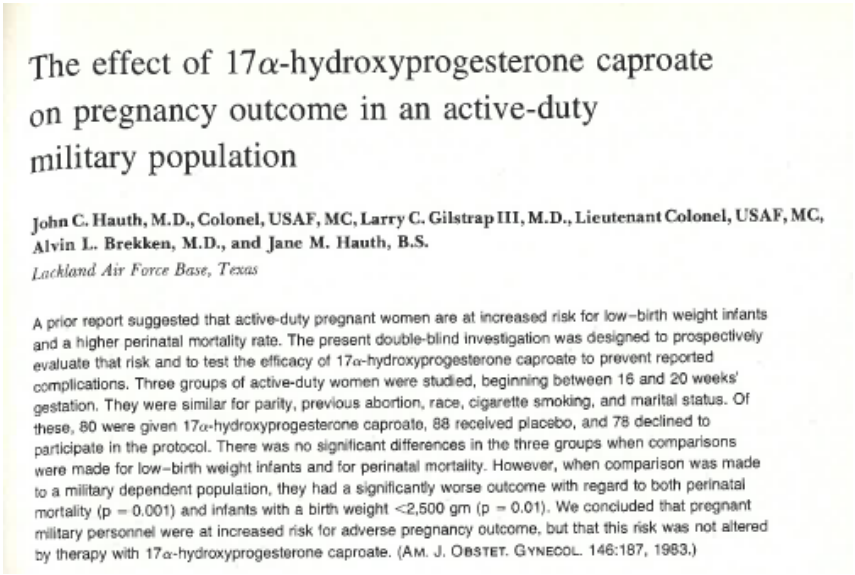
- Randomized, double blind study
- 43 high risk patients
- Dose: 250 mg IM weekly until 37 weeks or delivery

- Results: 8.5% of patients treated with 17-OHPC delivered prematurely, 41% of those in the placebo group did the same; mean duration of pregnancy, mean birth weight were greater in treatment group

- Conclusion: "*possible obstetric use for this drug*"

Johnson et al NEJM. 1975

Progestogen use in recurrent spontaneous preterm birth prevention



The effect of 17α-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population

John C. Hauth, M.D., Colonel, USAF, MC, Larry C. Gilstrap III, M.D., Lieutenant Colonel, USAF, MC, Alvin L. Brekken, M.D., and Jane M. Hauth, B.S.
Lackland Air Force Base, Texas

A prior report suggested that active-duty pregnant women are at increased risk for low-birth weight infants and a higher perinatal mortality rate. The present double-blind investigation was designed to prospectively evaluate that risk and to test the efficacy of 17α-hydroxyprogesterone caproate to prevent reported complications. Three groups of active-duty women were studied, beginning between 16 and 20 weeks' gestation. They were similar for parity, previous abortion, race, cigarette smoking, and marital status. Of these, 80 were given 17α-hydroxyprogesterone caproate, 88 received placebo, and 78 declined to participate in the protocol. There was no significant differences in the three groups when comparisons were made for low-birth weight infants and for perinatal mortality. However, when comparison was made to a military dependent population, they had a significantly worse outcome with regard to both perinatal mortality ($p = 0.001$) and infants with a birth weight <2,500 gm ($p = 0.01$). We concluded that pregnant military personnel were at increased risk for adverse pregnancy outcome, but that this risk was not altered by therapy with 17α-hydroxyprogesterone caproate. (Am. J. Obstet. Gynecol. 146:187, 1983.)

Conclusion:
weekly injections of 17-alpha hydroxyprogesterone caproate "did not alter risk" of adverse pregnancy outcome including preterm birth

Table II. Pregnancy complications in the three groups of active-duty women

	17α-Hydroxyprogesterone caproate, 80 (%)	*Placebo, 88 (%)*	*Declined, 78 (%)*
Pregnancy-induced hypertension	12.5*	13.6*	3.0*
Small for gestational age	3.8	4.5	2.6
Infant weight <2,500 gm	7.5	9.0	11.5
Major congenital defects	3.8	2.3	2.6
Postterm pregnancy	16.0	10.0	18.0
Premature labor	6.3	5.7	10.2

*p = 0.01.

Hauth et al. AJOG. 1983

Progestogen use in recurrent spontaneous preterm birth prevention

By letter dated September 13, 1999, BMS requested withdrawal of NDA 10–347 for DELALUTIN (hydroxyprogesterone caproate) injection and stated that the drug product had not been marketed for several years.

In the Federal Register of September 13, 2000 (65 FR 55264), **FDA announced that it was withdrawing approval** of NDA 10–347 and NDA 16–911, effective September 30, 2000.

Progestogen use in recurrent spontaneous preterm birth prevention

British Journal of Obstetrics and Gynaecology
February 1990, Vol. 97, pp. 149–154

Progestogen administration in pregnancy may prevent preterm delivery

MARC J. N. C. KEIRSE

Summary. Two recently published meta-analyses of controlled trials of a wide variety of progestational agents, used in pregnancy (Daya 1989; Goldstein *et al.* 1989), prompted this third meta-analysis of placebo-controlled trials involving the prophylactic use of a single agent, 17α-hydroxyprogesterone caproate. Of seven relevant published reports of controlled trials, six had involved women considered to be at high risk of miscarriage or preterm birth. This analysis provides no support for the view that 17α-hydroxyprogesterone caproate protects against miscarriage, but suggests that it does reduce the occurrence of preterm birth. The latter effect was reflected in a reduced rate of low birthweight babies, but not in a statistically significant reduction in perinatal mortality and morbidity. The difference between this meta-analysis and the two earlier meta-analyses illustrates the problems both of selective subgrouping and of comprehensive pooling of data from small trials.

A communication by Allen *et al.* (1935) reported their agreement to use henceforth only the name progesterone for the pregnancy-maintaining hormone extracted from corpora lutea previously known as luteosteron and progestin. Their communication appeared on the same page that introduced 'prostaglandin' for the first time (von Euler 1935). It was not to be anticipated, however, that 50 years later there would be wide consensus on the effects of prostaglandin administration, but not on the effects of progesterone administration in pregnancy.

Recently, Daya (1989) and Goldstein *et al.* (1989) reported separate meta-analyses assessing the effects of progestogen administration in pregnancy, but reached contradictory conclusions. Daya (1989) concluded that the available evidence supported a beneficial effect on the risk of early pregnancy failure, whereas Goldstein *et al.* (1989) concluded that the data did not support such a conclusion.

One may be inclined to attribute this difference in opinion to semantics: Daya (1989) reported on 'progesterone'; whereas Goldstein *et al.* (1989) reported on 'progestational agents'. This is not so, however. Only one of the three studies included by Daya (1989), the trial of Swyer and Daley (1953), actually used progesterone. Daya's conclusions are thus based on as wide an array of agents as those of Goldstein *et al.* (1989).

Because there are large differences among the many agents considered to be progestational on the basis of pharmacological tests, I have conducted a third, more restricted meta-analysis using data from all placebo-controlled trials involving prophylactic use of the most fully studied progestational agent, 17α-hydroxyprogesterone caproate.

Department of Obstetrics and Gynaecology, Leiden University, The Netherlands, and University of Leuven, Belgium
MARC J. N. C. KEIRSE

Correspondence: M. J. N. C. Keirse, Vrouwenkliniek, Leiden University Hospital, Postbus 9600, NL-2300 RC Leiden, The Netherlands

Materials and methods

Placebo-controlled trials of 17α-hydroxyproges-

Table 2. Effects of 17α-hydroxyprogesterone caproate administration in pregnancy on various pregnancy outcomes

Pregnancy outcome and study	17α-hydroxy-progesterone	Placebo	Odds ratio (95% CI)
Miscarriage			
Shearman (1968)	5/27	5/23	0·82 (0·21– 3·25)
Yemini *et al.* (1985)	8/39	3/40	2·92 (0·82–10·36)
LeVine (1964)	3/15	7/15	0·31 (0·07– 1·39)
Johnson *et al.* (1975)*	3/23	0/27	9·64 (0·95–97·98)
Typical odds ratio			1·30 (0·61– 2·74)
Prelabour rupture of membranes			
Hartikainen-Sorri *et al.* (1980)	5/39	2/38	2·47 (0·53–11·55)
Yemini *et al.* (1985)	2/39	3/40	0·67 (0·11– 4·08)
Typical odds ratio			1·42 (0·44– 4·59)
Preterm labour			
Hauth *et al.* (1983)	5/80	5/88	1·11 (0·31– 3·96)
Yemini *et al.* (1985)	9/39	22/40	0·27 (0·11– 0·65)
Typical odds ratio			0·43 (0·20– 0·89)
Preterm birth			
Papiernik-Berkhauer (1970)†	2/50	9/49	0·24 (0·07– 0·82)
Hartikainen-Sorri *et al.* (1980)‡	15/39	9/38	1·97 (0·76– 5·15)
Yemini *et al.* (1985)	5/39	14/40	0·30 (0·11– 0·84)
LeVine (1964)§	2/15	3/15	0·63 (0·10– 4·15)
Johnson *et al.* (1975)	2/18	12/25	0·19 (0·05– 0·70)
Typical odds ratio			0·50 (0·30– 0·85)
[illegible]			
Hauth *et al.* (1983)	6/80	8/88	0·81 (0·27– 2·42)
Papiernik-Berkhauer (1970)	2/50	8/49	0·26 (0·07– 0·96)
Yemini *et al.* (1985)	5/39	14/40	0·30 (0·11– 0·84)
LeVine (1964)	3/15	2/15	1·59 (0·24–10·51)
Johnson *et al.* (1975)	4/18	11/26	0·42 (0·12– 1·46)
Typical odds ratio			0·46 (0·27– 0·80)
Perinatal death excluding lethal malformation			
Hauth *et al.* (1983)	3/80	3/88	1·10 (0·22– 5·61)
Papiernik-Berkhauer (1970)	0/49	0/47	1·00
Hartikainen-Sorri *et al.* (1980)	4/78	2/76	1·94 (0·38– 9·87)
Yemini *et al.* (1985)	0/39	0/40	1·00
LeVine (1964)	1/15	0/15	7·39 (0·15–99·99)
Johnson *et al.* (1975)	0/18	7/26	0·14 (0·03– 0·71)
Typical odds ratio			0·76 (0·31– 1·90)
Respiratory distress syndrome			
Hartikainen-Sorri *et al.* (1980)	10/78	4/76	2·48 (0·83– 7·42)
Yemini *et al.* (1985)	1/39	4/40	0·29 (0·05– 1·75)
Typical odds ratio			1·39 (0·54– 3·54)
Hyperbilirubinaemia			
Hartikainen-Sorri *et al.* (1980)	8/78	8/76	0·97 (0·35– 2·73)
Yemini *et al.* (1985)	4/39	11/40	0·33 (0·11– 1·01)
Typical odds ratio			0·59 (0·28– 1·26)

Keirse MJN. BJOG. 1990

Maternal-Fetal Medicine Units Network, 2003

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*

ABSTRACT

BACKGROUND
Women who have had a spontaneous preterm delivery are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery.

METHODS
We conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle.

RESULTS
Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

CONCLUSIONS
Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

From Wake Forest University, Winston-Salem, N.C. (P.J.M.); the National Institute of Child Health and Human Development, Bethesda, Md. (M.K., C.Y.S.); the Biostatistics Center, George Washington University, Rockville, Md. (E.T.); Wayne State University, Detroit (M.P.D.); the University of Tennessee, Memphis (B.S.); the University of Chicago, Chicago (A.H.M.); the University of Alabama, Birmingham (J.C.H.); the University of Cincinnati, Cincinnati, and Columbia University, New York (M.M.); the University of Utah, Salt Lake City (M.W.V.); the University of Texas Southwestern Medical Center, Dallas (K.J.L.); the University of Pittsburgh, Pittsburgh (S.N.C.); Ohio State University, Columbus (J.D.I.); Thomas Jefferson University, Philadelphia (R.J.W.); the University of Texas, San Antonio (D.C.); the University of Miami, Miami (M.J.O.); Brown University, Providence, R.I. (M.C.); Case Western Reserve University, Cleveland (B.M.); the University of Texas, Houston (S.M.R.); the University of North Carolina, Chapel Hill (J.M.T.); and Northwestern University, Chicago (A.M.P.). Address reprint requests to Dr. Meis at the Department of Obstetrics and Gynecology, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, or at pmeis@wfubmc.edu.

*Other members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are listed in the Appendix.

N Engl J Med 2003;348:2379-85.

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no. (%)		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)

Meis et al NEJM. 2003

Maternal-Fetal Medicine Units Network, 2003

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*

ABSTRACT

BACKGROUND
Women who have had a spontaneous preterm delivery are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery.

METHODS
We conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle.

RESULTS
Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

CONCLUSIONS
Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

From Wake Forest University, Winston-Salem, N.C. (P.J.M.); the National Institute of Child Health and Human Development, Bethesda, Md. (M.K., C.Y.S.); the Biostatistics Center, George Washington University, Rockville, Md. (E.T.); Wayne State University, Detroit (M.P.D.); the University of Tennessee, Memphis (B.S.); the University of Chicago, Chicago (A.H.M.); the University of Alabama, Birmingham (J.C.H.); the University of Utah, Salt Lake City (M.W.V.); the University of Cincinnati, Cincinnati, and Columbia University, New York (M.M.); the University of Utah, Salt Lake City (M.W.V.); the University of Texas Southwestern Medical Center, Dallas (K.J.L.); the University of Pittsburgh, Pittsburgh (S.N.C.); Ohio State University, Columbus (J.D.I.); Thomas Jefferson University, Philadelphia (R.J.W.); the University of Texas, San Antonio (D.C.); the University of Miami, Miami (M.J.O.); Brown University, Providence, R.I. (M.C.); Case Western Reserve University, Cleveland (B.M.); the University of Texas, Houston (S.M.R.); the University of North Carolina, Chapel Hill (J.M.T.); and Northwestern University, Chicago (A.M.P.). Address reprint requests to Dr. Meis at the Department of Obstetrics and Gynecology, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, or at pmeis@wfubmc.edu.

*Other members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are listed in the Appendix.

N Engl J Med 2003;348:2379-85.

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no. (%)		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)

Meis et al NEJM. 2003

Maternal-Fetal Medicine Units Network, 2003

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*

ABSTRACT

BACKGROUND
Women who have had a spontaneous preterm delivery are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery.

METHODS
We conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle.

RESULTS
Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

CONCLUSIONS
Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

From Wake Forest University, Winston-Salem, N.C. (P.J.M.); the National Institute of Child Health and Human Development, Bethesda, Md. (M.K., C.Y.S.); the Biostatistics Center, George Washington University, Rockville, Md. (E.T.); Wayne State University, Detroit (M.P.D.); the University of Tennessee, Memphis (B.S.); the University of Chicago, Chicago (A.H.M.); the University of Alabama, Birmingham (J.C.H.); the University of Cincinnati, Cincinnati, and Columbia University, New York (M.M.); the University of Utah, Salt Lake City (M.W.V.); the University of Texas Southwestern Medical Center, Dallas (K.J.L.); the University of Pittsburgh, Pittsburgh (S.N.C.); Ohio State University, Columbus (J.D.I.); Thomas Jefferson University, Philadelphia (R.J.W.); the University of Texas, San Antonio (D.C.); the University of Miami, Miami (M.J.O.); Brown University, Providence, R.I. (M.C.); Case Western Reserve University, Cleveland (B.M.); the University of Texas, Houston (S.M.R.); the University of North Carolina, Chapel Hill (J.M.T.); and Northwestern University, Chicago (A.M.P.). Address reprint requests to Dr. Meis at the Department of Obstetrics and Gynecology, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, or at pmeis@wfubmc.edu.

*Other members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are listed in the Appendix.

N Engl J Med 2003;348:2379-85.

Outcome	Progesterone Group (N=306)	Placebo Group (N=153)	Relative Risk (95% CI)
	no. (%)		
Delivery before 37 wk of gestation	111 (36.3)	84 (54.9)	0.66 (0.54–0.81)
Spontaneous	90 (29.4)	69 (45.1)	0.65 (0.51–0.83)
Indicated because of complications	21 (6.9)	15 (9.8)	0.70 (0.37–1.32)
Black women	64 (35.4)	47 (52.2)	0.68 (0.51–0.90)
Nonblack women	47 (37.6)	37 (58.7)	0.64 (0.47–0.87)
Delivery before 35 wk of gestation	63 (20.6)	47 (30.7)	0.67 (0.48–0.93)
Delivery before 32 wk of gestation	35 (11.4)	30 (19.6)	0.58 (0.37–0.91)

Meis et al NEJM. 2003

Maternal-Fetal Medicine Units Network, 2003

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*

ABSTRACT

BACKGROUND

Women who have had a spontaneous preterm delivery are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery.

METHODS

We conducted a double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery. Women were enrolled at 19 clinical centers at 16 to 20 weeks of gestation and randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle.

RESULTS

Base-line characteristics of the 310 women in the progesterone group and the 153 women in the placebo group were similar. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]). Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen.

CONCLUSIONS

Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

From Wake Forest University, Winston-Salem, N.C. (P.J.M.); the National Institute of Child Health and Human Development, Bethesda, Md. (M.K., C.Y.S.); the Biostatistics Center, George Washington University, Rockville, Md. (E.T.); Wayne State University, Detroit (M.P.D.); the University of Tennessee, Memphis (B.S.); the University of Chicago, Chicago (A.H.M.); the University of Alabama, Birmingham (J.C.H.); the University of Cincinnati, Cincinnati, and Columbia University, New York (M.M.); the University of Utah, Salt Lake City (M.W.V.); the University of Texas Southwestern Medical Center, Dallas (K.J.L.); the University of Pittsburgh, Pittsburgh (S.N.C.); Ohio State University, Columbus (J.D.I.); Thomas Jefferson University, Philadelphia (R.J.W.); the University of Texas, San Antonio (D.C.); the University of Miami, Miami (M.J.O.); Brown University, Providence, R.I. (M.C.); Case Western Reserve University, Cleveland (B.M.); the University of Texas, Houston (S.M.R.); the University of North Carolina, Chapel Hill (J.M.T.); and Northwestern University, Chicago (A.M.P.). Address reprint requests to Dr. Meis at the Department of Obstetrics and Gynecology, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, or at pmeis@wfubmc.edu.

*Other members of the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network are listed in the Appendix.

N Engl J Med 2003;348:2379-85.

Table 1. Characteristics of the 463 Women at Randomization.*

Characteristic	Progesterone Group (N=310)	Placebo Group (N=153)
Duration of gestation at the time of qualifying delivery — wk	30.6±4.6	31.3±4.2
No. of previous preterm deliveries	1.4±0.7	1.6±0.9†
>1 Previous preterm delivery — no. (%)	86 (27.7)	63 (41.2)
≥1 Previous term deliveries — no. (%)	153 (49.4)	71 (46.4)
Duration of gestation at randomization — wk	18.4±1.4	18.4±1.4
Age — yr	26.0±5.6	26.5±5.4
Race or ethnic group — no. (%)‡		
Non-Hispanic black	183 (59.0)	90 (58.8)
Non-Hispanic white	79 (25.5)	34 (22.2)
Hispanic	43 (13.9)	26 (17.0)
Asian	2 (0.6)	1 (0.7)
Other	3 (1.0)	2 (1.3)
Marital status — no. (%)		
Married or living with partner	159 (51.3)	71 (46.4)
Never married	119 (38.4)	64 (41.8)
Divorced, widowed, or separated	32 (10.3)	18 (11.8)
Body-mass index before pregnancy§	26.9±7.9	26.0±7.0
Yr of education	11.7±2.3	11.9±2.3
Smoking during pregnancy — no. (%)	70 (22.6)	30 (19.6)
Alcohol use during pregnancy — no. (%)	27 (8.7)	10 (6.5)
Substance use during pregnancy — no. (%)	11 (3.5)	4 (2.6)

Meis et al NEJM. 2003

Maternal-Fetal Medicine Units Network, 2003

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate

TO THE EDITOR: After reading the article by Meis et al. (June 12 issue),[1] we strongly discourage practitioners from using 17 alpha-hydroxyprogesterone caproate in the care of women who have had pre-

Although initially enthusiastic about the results, which showed a risk reduction among the women who received 17 alpha-hydroxyprogesterone caproate, we were concerned about the high rate of recurrent preterm delivery among the women who received placebo. The Methods section states that the placebo was castor oil. Ricinoleic acid, the active ingredient in castor oil, is a known uterine stimulant.[2,3] Castor oil is used to induce labor.[4] We speculate that the high rate of preterm delivery in the placebo group was due to the injections of castor oil. If the study medication was given in castor oil (the authors do not say whether it was), then any beneficial effect may have been negated by the vehicle. If not, then the rate of preterm delivery among those receiving 17 alpha-hydroxyprogesterone caproate was no better than that in the historical controls.[5] We believe that practitioners should use caution before adopting this regimen for their patients at risk for preterm delivery.

Leo R. Brancazio, M.D.
Amy P. Murtha, M.D.
R. Phillps Heine, M.D.
Duke University Medical Center
Durham, NC 27710
branc020@mc.duke.edu

1. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.
2. Gao J, Sun N, Wang F, Hao N. Effect of castor oil-diet on the initiation of labor of pregnant rat. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 1998;20:367-70. (In Chinese.)
3. Gao J, Sun N, Wang F. Effects of castor oil-diet on the synthesis of prostaglandin E2 in pregnant rats. Zhongguo Fu Chan Ke Za Zhi 1999;34:147-9. (In Chinese.)
4. Garry D, Figueroa R, Guillaume J, Cucco V. Use of castor oil in pregnancies at term. Altern Ther Health Med 2000;6:77-9.
5. Iams JD, Newman RB, Thom EA, et al. Frequency of uterine contractions and the risk of spontaneous preterm delivery. N Engl J Med 2002;346:250-5.

THE AUTHORS REPLY: We used castor oil as the placebo injection because it was the vehicle for the 17 alpha-hydroxyprogesterone caproate medication and has been the vehicle used for 17 alpha-hydroxyprogesterone caproate since the production of the original drug (marketed as Delalutin). There is a long record of use of this drug during pregnancy without adverse effects.[1-3]

We considered the possibility that the placebo used in our trial might have an adverse effect and rejected this idea for several reasons. The high rate of preterm delivery among the women in the placebo group can be explained by their particularly strong risk factors for preterm delivery, with a mean duration of gestation at the time of the qualifying delivery of 31.3 weeks and a mean number of previous preterm deliveries of 1.6.

THIS WEEK'S LETTERS

Brancazio et al. NEJM. 2003

Progesterone is not the same as 17α-hydroxyprogesterone caproate: implications for obstetrical practice

Roberto Romero, MD, D. Med. Sci; Frank Z. Stanczyk, PhD

Clinicians[1-4] and professional organizations[3-7] commenting on the role of progestogens in the prevention of preterm birth have used the term *progesterone* interchangeably with 17α-hydroxyprogesterone caproate, implying that these two compounds are the same. Yet, there are chemical, biological, and pharmacologic differences between the two.[8,9] The clinical indications also differ. This Editorial will review the differences between the two compounds and propose that clinicians and investigators use the abbreviation *17-OHPC* (rather than 17P) to refer to 17α-hydroxyprogesterone caproate. The abbreviation 17-OHPC was first recommended by Dr Steven Caritis from the University of Pittsburgh and has been used in the American Journal of Obstetrics and Gynecology by Dr Caritis and his coauthors.

Progestogen and progestins: what is the difference?
A progestogen is a compound with progesterone-like action (natural or synthetic). This has been defined as the ability of a chemical agent to transform a proliferative into a secretory endometrium to support pregnancy. The term *progestins* refers to synthetic progestogens and, for the sake of clarity, should not be applied to natural progesterone (examples of progestins include medroxyprogesterone acetate, norethindrone, and levonorgestrel, which have been used as agents for contraception and hormone replacement).

Progestogens: natural or synthetic

Progestogens can be classified as natural or synthetic.[10-13] Natural compounds are those with chemical structures similar to those produced by living organisms. In contrast, synthetic progestogens (or progestins) are compounds generated in the laboratory whose structures have been modified and do not correspond to a naturally occurring steroid. Progesterone is a natural progestogen; 17α-hydroxyprogesterone caproate (17-OHPC) is synthetic (Table).[11,12]

Progesterone

Progesterone is a natural sex steroid produced by the corpus luteum and subsequently the placenta. The chemical structure is illustrated in the Figure. Csapo et al[14-19] demonstrated that progesterone was key for the support of pregnancy in the first trimester. The findings of Csapo et al were buttressed by the observation that progesterone receptor blockade leads to early pregnancy loss (eg, RU-486 or mifepristone administration).[20-25] Moreover, the administration of RU-486 to pregnant women in the third trimester results in cervical ripening and often the onset of labor.[24-27]

17α-hydroxyprogesterone caproate

17α-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestogen. The human body does not make the caproate molecule. Another name for caproate is "hexanoate," which is an ester derived from hexanoic (or caproic) acid.[28,29] The formula of 17-OHPC is displayed in the Figure. Some physicians have stated that 17-OHPC is found in goats. This seems to be a folktale, because the identification of this molecule from natural body fluids, tissues from goats, or any other living organism could not be confirmed in a literature search.

17P: an abbreviation that has led to confusion

The abbreviation *17P* has been used by many (including one of the authors, R.R.) to refer to 17-OHPC.[1,2,5,7,30-41] This has been unfortunate because the term *17P* does not convey information about the presence of the caproate molecule. Indeed, 17P has also been used to refer to 17α-hydroxyprogesterone (17OHP), which is a naturally occurring steroid produced by the ovary with weak progestational activity. Indeed, a popular source states that "17P or 17.P or 17-P" may refer to 17-hydroxyprogesterone."[42]

The extent of the confusion is such that, at national scientific meetings, some academicians have represented that 17P is a naturally occurring steroid produced by the human placenta. This view has been expressed on websites that are intended to inform patients.[43] This is not accurate. The source of this misconception appears to be the use of the term *17P*. The confusion extends to an agency with expertise in the review of drugs; this organization has used the term *17-OHP* when referring to 17-OHPC.[44]

Differences between progesterone and 17α-hydroxyprogesterone caproate

Progesterone and 17-OHPC have different physiologic properties and pharmacologic profiles. Moreover, there are different indications for their use in obstetrics.

From the Perinatology Research Branch, NICHD/NIH/DHHS, Detroit, MI and Bethesda, MD (Dr Romero); and the Departments of Obstetrics and Gynecology and Preventive Medicine, Keck School of Medicine of University of Southern California, Los Angeles, CA (Dr Stanczyk).

Supported, in part, by the Perinatology Research Branch, Division of Intramural Research, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services.
The authors report no conflict of interest.

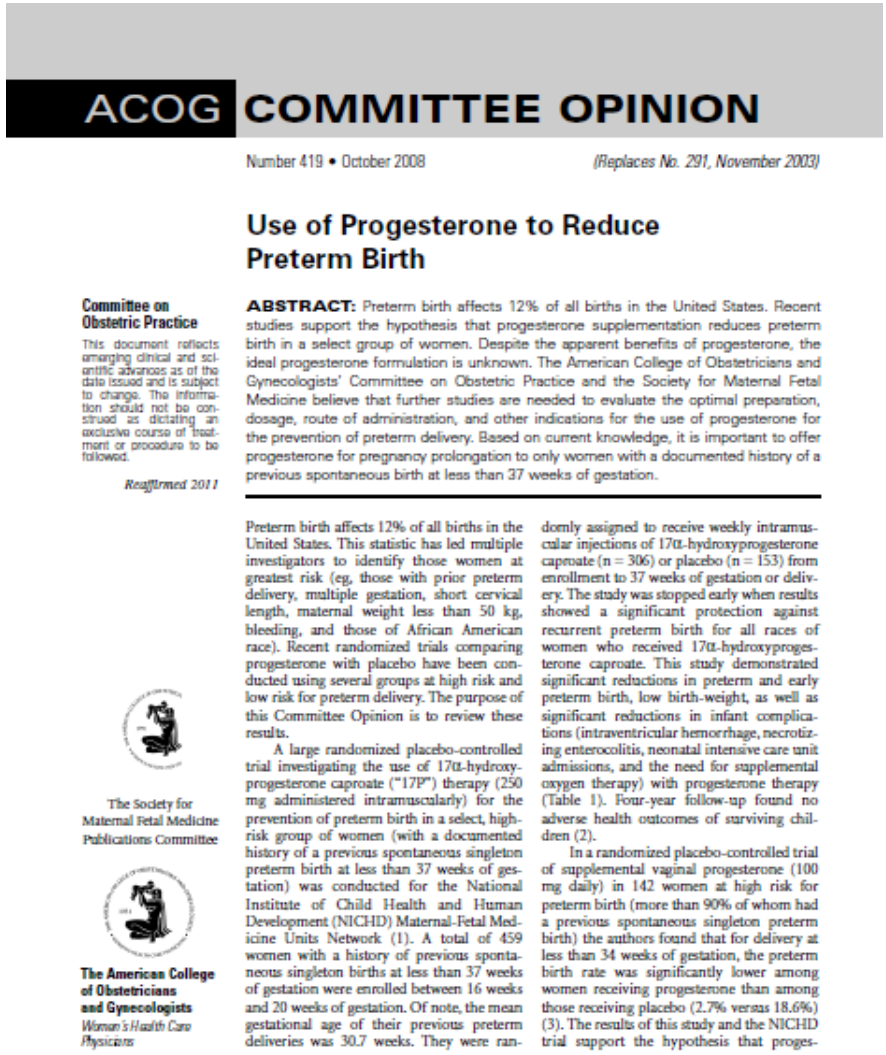
Correspondence: Roberto Romero, MD, D. Med. Sci, Perinatology Research Branch, NICHD/NIH/DHHS, Detroit, MI and Bethesda, MD. romeror@mail.nih.gov.

0002-9378/free
© 2013 Published by Mosby, Inc.
http://dx.doi.org/10.1016/j.ajog.2013.04.027

One of the questions raised during the review of the RCT by Meis et al[1] was the high rate of preterm delivery in the placebo group of the trial, which was 54.9%.[69] This has been considered as an unexpectedly high rate of preterm delivery for patients with a previous preterm delivery. This question was raised by the medical office of the Food and Drug Administration (FDA), based upon the first phase of this trial in which 17-OHPC was compared to placebo and the rate of preterm delivery in the placebo group was 36%. This first phase of the study was called "17P-IF-001" 150 subjects were randomized, 104 subjects had delivered, and there were 65 patients allocated to 17-OHPC and 39 to placebo. This first phase of the study had to be stopped because of problems with the manufacturing of 17-OHPC.[44] The key question is why in the first phase of the study, the rate of preterm delivery in the placebo group was 36% and in the subsequent trial (Meis et al[1]) by the same investigators it was 54.9%. Iams has proposed that the high rate of preterm delivery in the placebo group can be attributed to the inclusion of a subset of women who were at particularly high risk for preterm delivery because of a history of early preterm birth, ethnic origin, or who were highly motivated to take a weekly injection of 17-OHPC.[70] However, if the positive findings of the trial are due to the effect of 17-OHPC in this particular subgroup of patients, the external validity or generalizability to patients who do not have the same risk profile would be open to question.[71] Specifically, should 17-OHPC be used in women with a history of preterm birth but who do not fit the "high risk profile" that has been invoked to justify the high rate of preterm delivery in the control group? The only way to resolve this question is to replicate the findings with another trial (see below).

Romero, Stanczyk. AJOG. 2013

Role of progestogen in pregnancy, 2008



ACOG COMMITTEE OPINION

Number 419 • October 2008 (Replaces No. 291, November 2003)

Use of Progesterone to Reduce Preterm Birth

Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Reaffirmed 2011

The Society for Maternal Fetal Medicine Publications Committee

The American College of Obstetricians and Gynecologists
Women's Health Care Physicians

ABSTRACT: Preterm birth affects 12% of all births in the United States. Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women. Despite the apparent benefits of progesterone, the ideal progesterone formulation is unknown. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to evaluate the optimal preparation, dosage, route of administration, and other indications for the use of progesterone for the prevention of preterm delivery. Based on current knowledge, it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation.

Preterm birth affects 12% of all births in the United States. This statistic has led multiple investigators to identify those women at greatest risk (eg, those with prior preterm delivery, multiple gestation, short cervical length, maternal weight less than 50 kg, bleeding, and those of African American race). Recent randomized trials comparing progesterone with placebo have been conducted using several groups at high risk and low risk for preterm delivery. The purpose of this Committee Opinion is to review these results.

A large randomized placebo-controlled trial investigating the use of 17α-hydroxyprogesterone caproate ("17P") therapy (250 mg administered intramuscularly) for the prevention of preterm birth in a select, high-risk group of women (with a documented history of a previous spontaneous singleton preterm birth at less than 37 weeks of gestation) was conducted for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (1). A total of 459 women with a history of previous spontaneous singleton births at less than 37 weeks of gestation were enrolled between 16 weeks and 20 weeks of gestation. Of note, the mean gestational age of their previous preterm deliveries was 30.7 weeks. They were randomly assigned to receive weekly intramuscular injections of 17α-hydroxyprogesterone caproate (n = 306) or placebo (n = 153) from enrollment to 37 weeks of gestation or delivery. The study was stopped early when results showed a significant protection against recurrent preterm birth for all races of women who received 17α-hydroxyprogesterone caproate. This study demonstrated significant reductions in preterm and early preterm birth, low birth-weight, as well as significant reductions in infant complications (intraventricular hemorrhage, necrotizing enterocolitis, neonatal intensive care unit admissions, and the need for supplemental oxygen therapy) with progesterone therapy (Table 1). Four-year follow-up found no adverse health outcomes of surviving children (2).

In a randomized placebo-controlled trial of supplemental vaginal progesterone (100 mg daily) in 142 women at high risk for preterm birth (more than 90% of whom had a previous spontaneous singleton preterm birth) the authors found that for delivery at less than 34 weeks of gestation, the preterm birth rate was significantly lower among women receiving progesterone than among those receiving placebo (2.7% versus 18.6%) (3). The results of this study and the NICHD trial support the hypothesis that proges-

ACOG Com Opinion. 2008

Role of progestogen in pregnancy in TWINS?

Role of progestogen in pregnancy in TWINS? NO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of 17 Alpha-Hydroxyprogesterone Caproate to Prevent Prematurity in Twins

Dwight J. Rouse, M.D., Steve N. Caritis, M.D., Alan M. Peaceman, M.D., Anthony Sciscione, D.O., Elizabeth A. Thom, Ph.D., Catherine Y. Spong, M.D., Michael Varner, M.D., Fergal Malone, M.D., Jay D. Iams, M.D., Brian M. Mercer, M.D., John Thorp, M.D., Yoram Sorokin, M.D., Marshall Carpenter, M.D., Julie Lo, M.D., Susan Ramin, M.D., Margaret Harper, M.D., and Garland Anderson, M.D., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

ABSTRACT

BACKGROUND

In singleton gestations, 17 alpha-hydroxyprogesterone caproate (17P) has been shown to reduce the rate of recurrent preterm birth. This study was undertaken to evaluate whether 17P would reduce the rate of preterm birth in twin gestations.

METHODS

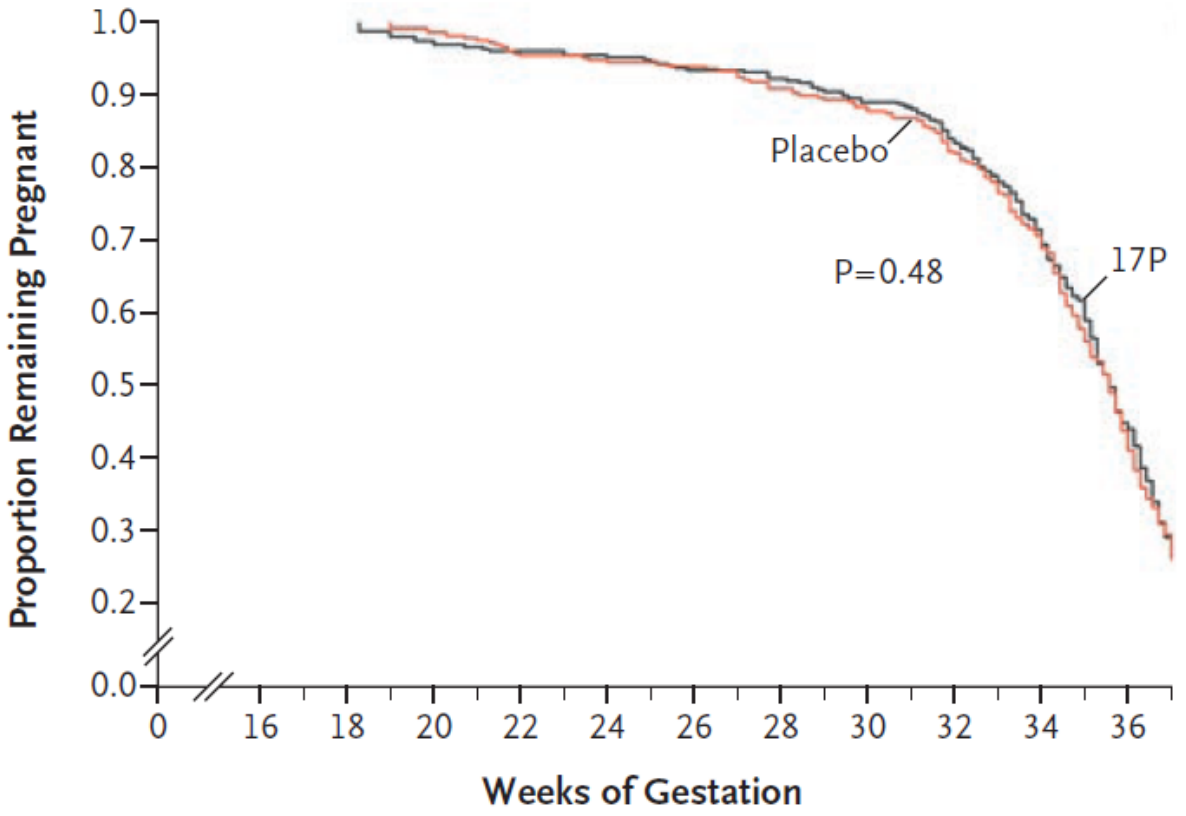
We performed a randomized, double-blind, placebo-controlled trial in 14 centers. Healthy women with twin gestations were assigned to weekly intramuscular injections of 250 mg of 17P or matching placebo, starting at 16 to 20 weeks of gestation and ending at 35 weeks. The primary study outcome was delivery or fetal death before 35 weeks of gestation.

RESULTS

Six hundred sixty-one women were randomly assigned to treatment. Baseline demographic data were similar in the two study groups. Six women were lost to follow-up; data from 655 were analyzed (325 in the 17P group and 330 in the placebo group). Delivery or fetal death before 35 weeks occurred in 41.5% of pregnancies in the 17P group and 37.3% of those in the placebo group (relative risk, 1.1; 95% confidence interval [CI], 0.9 to 1.3). The rate of the prespecified composite outcome of serious adverse fetal or neonatal events was 20.2% in the 17P group and 18.0% in the placebo group (relative risk, 1.1; 95% CI, 0.9 to 1.5). Side effects of the injections were frequent in both groups, occurring in 65.9% and 64.4% of subjects, respectively (P=0.69), but were generally mild and limited to the injection site.

CONCLUSIONS

Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with twin gestations. (ClinicalTrials.gov number, NCT00099164.)



No. of Pregnancies at Risk											
Placebo	5	78	201	313	311	308	298	290	270	232	144
17P	6	74	198	327	325	317	312	301	284	241	151

Rouse et al. NEJM. 2007

Role of progestogen in pregnancy in TRIPLETS?

Role of progestogen in pregnancy in TRIPLETS? NO

Prevention of Preterm Birth in Triplets Using 17 Alpha-Hydroxyprogesterone Caproate

A Randomized Controlled Trial

*Steve N. Caritis, MD, Dwight J. Rouse, MD, Alan M. Peaceman, MD, Anthony Sciscione, MD, Valerija Momirova, MS, Catherine Y. Spong, MD, Jay D. Iams, MD, Ronald J. Wapner, MD, Michael Varner, MD, Marshall Carpenter, MD, Julie Lo, MD, John Thorp, MD, Brian M. Mercer, MD, Yoram Sorokin, MD, Margaret Harper, MD, Susan Ramin, MD, and Garland Anderson, MD, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Maternal–Fetal Medicine Units Network (MFMU)**

OBJECTIVE: To assess whether 17 alpha-hydroxyprogesterone caproate reduces the rate of preterm birth in women carrying triplets.

METHODS: We performed this randomized, double-blinded, placebo-controlled trial in 14 centers. Healthy women with triplets were randomly assigned to weekly intramuscular injections of either 250 mg of 17 alpha-hydroxyprogesterone caproate or matching placebo, starting at 16–20 weeks and ending at delivery or 35 weeks of gestation. The primary study outcome was delivery or fetal loss before 35 weeks.

RESULTS: One hundred thirty-four women were assigned, 71 to 17 alpha-hydroxyprogesterone caproate and 63 to placebo; none were lost to follow-up. Baseline demographic data were similar in the two groups. The proportion of women experiencing the primary outcome (a composite of delivery or fetal loss before 35 0/7 weeks) was similar in the two treatment groups: 83% of pregnancies in the 17 alpha-hydroxyprogesterone caproate group and 84% in the placebo group, relative risk 1.0, 95% confidence interval 0.9–1.1. The lack of benefit of 17 alpha-hydroxyprogesterone caproate was evident regardless of the conception method or whether a gestational age cutoff for delivery was set at 32 or 28 weeks.

CONCLUSION: Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with triplet gestations.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00099164

(Obstet Gynecol 2009;113:285–92)

LEVEL OF EVIDENCE: I

Infants delivered before term account for the vast majority of perinatal mortality and morbidity. Among triplets, 45% deliver before 32 weeks of gestation, and perinatal mortality is 59 in 1,000 compared with 4 in 1,000 live births among singleton gestations delivered at term.[1,2] Thus, the societal burden of prematurity and its attendant complications are high among fetuses from multifetal gestation. This

*For the other members of the NICHD MFMU who participated in this study, see the Appendix online at http://links.lww.com/A643.

From the Departments of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, Pennsylvania; the Center for Women's Reproductive Health, University of Alabama at Birmingham, Birmingham, Alabama; Northwestern University, Chicago, Illinois; Drexel University, Philadelphia, Pennsylvania; the George Washington University Biostatistics Center, Washington, DC; Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland; Ohio State University, Columbus, Ohio; Columbia University, New York, New York; University of Utah, Salt Lake City, Utah; Brown University, Providence, Rhode Island; University of Texas Southwestern Medical Center, Dallas, Texas; University of North Carolina, Chapel Hill, North Carolina; Case Western University, Cleveland, Ohio; Wayne State University, Detroit, Michigan; Wake Forest University, Winston-Salem, North Carolina; University of Texas at Houston, Houston, Texas; and University of Texas Medical Branch, Galveston, Texas.

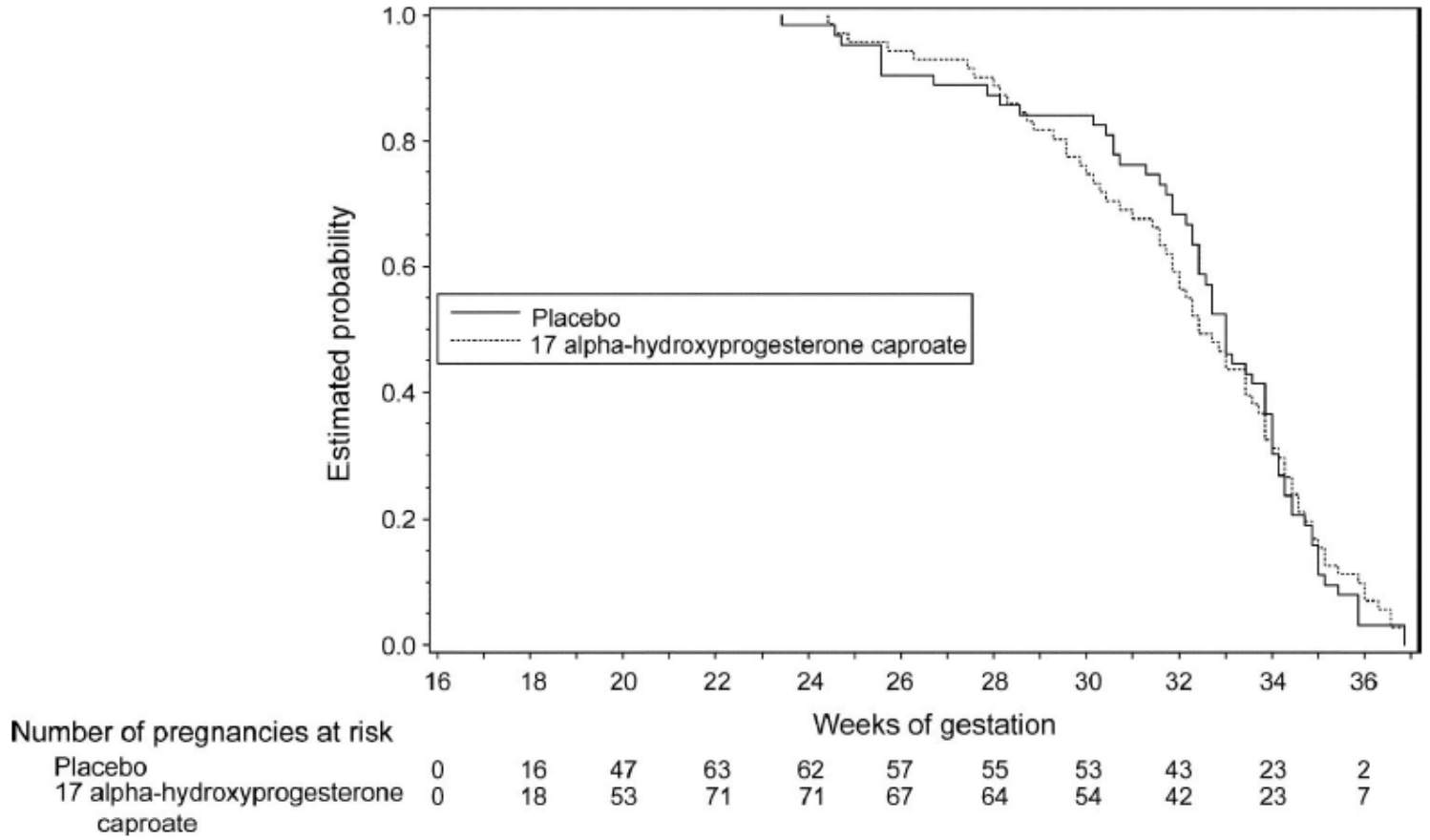
Supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, (HD21410; HD27869; HD40512; HD27915; HD40485; HD34208; HD40500; HD34116; HD40560; HD40544; HD27917; HD27860; HD40545; HD53097; HD36801; HD34136).

The authors thank subcommittee members Elizabeth Thom, PhD, for protocol/data management and statistical analysis and Allison Northen, RN, and Margaret Cotroneo, RN, for protocol development and coordination between clinical research centers. The authors also thank Joyce A. Martin, MPH, National Center for Health Statistics, who supplied U.S. natality and infant mortality data.

Corresponding author: Steve N. Caritis, 300 Halket Street, Room 2229, Pittsburgh, PA 15213; e-mail: scaritis@mail.magee.edu.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/09



Caritis et al. Obstet Gynecol. 2009

UTSouthwestern Medical Center

Role of progestogen in pregnancy AFTER RUPTURE OF MEMBRANES?

Role of progestogen in pregnancy AFTER RUPTURE OF MEMBRANES? NO

OBSTETRICS

Women with preterm premature rupture of the membranes do not benefit from weekly progesterone

Christian M. Briery, MD; Edward W. Veillon, MD; Chad K. Klauser, MD; Rick W. Martin, MD; Everett F. Magann, MD; Suneet P. Chauhan, MD; John C. Morrison, MD

OBJECTIVE: We sought to determine if 17-alpha-hydroxyprogesterone (17P) extends gestation vs placebo in women with preterm premature rupture of the membranes (PPROM).

STUDY DESIGN: Women with vertex presentations with PPROM, 20-30 weeks' gestation, were randomized to receive weekly 17P or placebo in an attempt to prolong the pregnancy. A total of 69 patients (17P, n = 33; placebo, n = 36) were randomized into this study.

RESULTS: Initial cervical dilatation, gestational age at enrollment, and interval to delivery were not different between the 2 groups ($P = .914$, .424, and .146, respectively). Time of randomization to delivery ($P = .250$), mode of delivery (relative risk, 1.16; 95% confidence interval, 0.66–2.06), and the neonatal outcome statistics of morbidity ($P = .820$) and mortality (relative risk, 1.28; 95% confidence interval, 0.59–2.75) were similar between the 2 groups.

CONCLUSION: In patients with PPROM, 17P did not extend gestation vs placebo and cannot be recommended for treatment in such women.

Key words: pregnancy prolongation, preterm premature rupture of membranes, progesterone

Cite this article as: Briery CM, Veillon EW, Klauser CK, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. Am J Obstet Gynecol 2011;204:54.e1-5.

Preterm premature rupture of the membranes (PPROM) complicates nearly 3% of all pregnancies and is responsible for one third of all premature births.[1] Rupture of the membranes is problematic, and is directly linked to prematurity-associated severe neonatal morbidity as well as mortality.[2] Overall 75% deliver within 1 week after rupture, but approximately 15% may extend gestation for several weeks.[2,3] Most commonly women with PPROM are placed in the hospital for antibiotics, steroids, and fetal testing. Delivery usually occurs around 34 weeks or when fetal-maternal indications require intervention.[3]

Progesterone has been shown to be important in maintaining pregnancy and preventing coordinated contractions by inhibiting the expression of cellular protein genes in the myometrium and inhibition of inflammatory factors.[4] Peltier et al[5] has also shown that proinflammatory cytokine production in cases of preterm birth are blunted by progesterone administration. Randomized clinical trials have shown that weekly injections of 17-alpha-hydroxyprogesterone (17P) or daily vaginal progesterone application reduce the number of preterm deliveries among high-risk women who had a prior spontaneous preterm birth.[6,7] In addition, 17P has been associated with a decrease in early preterm birth among women with a short cervix.[8] We propose that similar benefits may be seen in patients with PPROM when treated with 17P by inhibition of inflammation-associated preterm birth commonly seen in women with PPROM. To our knowledge, 17P has not been tested in women with prolonged PPROM.

The purpose of this study was to estimate whether 17P might extend gestation vs placebo in women with PPROM.

Materials and Methods

Patient recruitment in this placebo-controlled double-blind randomized clinical trial was carried out at a single site over a 4-year period (2003 through 2006) and complied with the CONSORT (Consolidated Standards of Reporting Trials) statement. The study was approved by the institutional review board (0239) at the University of Mississippi Medical Center and registered by Clinical Trials.gov (NCT00830765). Women who presented with singleton, vertex gestations to university's obstetric emergency area with a diagnosis of PPROM at 20-30 weeks' gestation, typically dated by ultrasound, were eligible for this study. Patients <24 weeks with PPROM were offered induction vs conservative management. These women were counseled and evaluated for pulmonary hypoplasia. Suspected amniorrhexis was confirmed by sonography, visualization of fluid coming from the cervix, and pos-

From the Department of Maternal-Fetal Medicine (Dr Briery), Willis-Knighton Health Sciences Center, Shreveport, LA; the Department of Obstetrics and Gynecology (Drs Veillon, Martin, and Morrison), University of Mississippi Medical Center, Jackson, MS; the Department of Obstetrics and Gynecology (Dr Klauser), Mount Sinai Medical Center, New York, NY; the Department of Obstetrics and Gynecology (Dr Magann), University of Arkansas for Medical Sciences, Little Rock, AR; and the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology (Dr Chauhan), Eastern Virginia School of Medicine, Norfolk, VA.

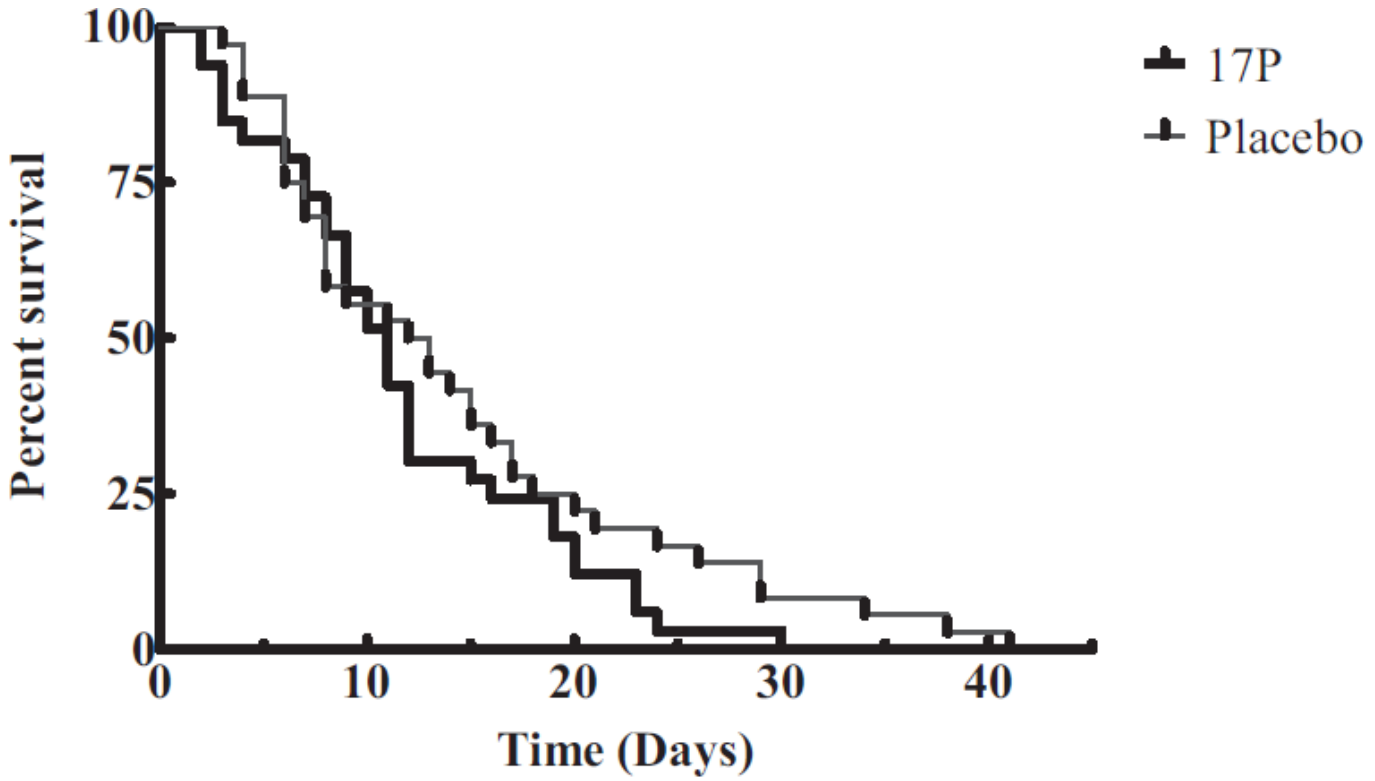
Presented at the 30th Annual Meeting of the Society for Maternal-Fetal Medicine, Chicago, IL, Feb. 1-6, 2010.

Received April 21, 2010; revised July 31, 2010; accepted Aug. 16, 2010.

Reprints not available from the authors.

0002-9378/$36.00

doi: 10.1016/j.ajog.2010.08.022



17P, 17-alpha-hydroxyprogesterone.

Briery CM et al. AJOG. 2011

UTSouthwestern Medical Center

Role of progestogen in pregnancy WITHOUT PRIOR PRETERM BIRTH?

Role of progestogen in pregnancy WITHOUT PRIOR PRETERM BIRTH? NO

RESEARCH www.AJOG.org

OBSTETRICS

17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm

William A. Grobman, MD, MBA; Elizabeth A. Thom, PhD; Catherine Y. Spong, MD; Jay D. Iams, MD; George R. Saade, MD; Brian M. Mercer, MD; Alan T. N. Tita, MD; Dwight J. Rouse, MD; Yoram Sorokin, MD; Ronald J. Wapner, MD; Kenneth J. Leveno, MD; Sean Blackwell, MD; M. Sean Esplin, MD; Jorge E. Tolosa, MD, MSCE; John M. Thorp Jr, MD; Steve N. Caritis, MD; J. Peter Van Dorsten, MD; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network

OBJECTIVE: We sought to evaluate whether 17 alpha-hydroxyprogesterone caproate (17-OHP) reduces preterm birth (PTB) in nulliparous women with a midtrimester cervical length (CL) <30 mm.

STUDY DESIGN: In this multicenter randomized controlled trial, nulliparous women with a singleton gestation between 16 and 22 3/7 weeks with an endovaginal CL <30 mm (<10th percentile in this population) were randomized to weekly intramuscular 17-OHP (250 mg) or placebo through 36 weeks. The primary outcome was PTB <37 weeks.

RESULTS: The frequency of PTB did not differ between the 17-OHP (n = 327) and placebo (n = 330) groups (25.1% vs 24.2%; relative risk, 1.03; 95% confidence interval, 0.79–1.35). There also was no difference in the composite adverse neonatal outcome (7.0% vs 9.1%; relative risk, 0.77; 95% confidence interval, 0.46–1.30).

CONCLUSION: Weekly 17-OHP does not reduce the frequency of PTB in nulliparous women with a midtrimester CL <30 mm.

Key words: nulliparous, progesterone, progestogen, short cervix

Cite this article as: Grobman WA, Thom EA, Spong CY, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. Am J Obstet Gynecol 2012;207:x.ex-x.ex.

Preterm birth (PTB) remains a major cause of morbidity and mortality worldwide. Not only is it responsible for approximately 50% of childhood blindness and one-third of cerebral palsy, but it increasingly has been implicated in adult morbidities, such as cardiovascular disease.[1,2] Correspondingly, PTB reduction has been a prominent public health goal and a focus of perinatal research.

★EDITORS' CHOICE★

From Northwestern University, Chicago, IL (Dr Grobman); George Washington University Biostatistics Center, Washington, DC (Dr Thom); Ohio State University, Columbus, OH (Dr Iams); University of Texas Medical Branch, Galveston, TX (Dr Saade); Case Western Reserve University–MetroHealth Medical Center, Cleveland, OH (Dr Mercer); University of Alabama at Birmingham, Birmingham, AL (Dr Tita); Brown University, Providence, RI (Dr Rouse); Wayne State University, Detroit, MI (Dr Sorokin); Columbia University, New York, NY (Dr Wapner); University of Texas Southwestern Medical Center, Dallas, TX (Dr Leveno); University of Texas Health Science Center at Houston, Houston, TX (Dr Blackwell); University of Utah Health Sciences Center, Salt Lake City, UT (Dr Esplin); Oregon Health and Science University, Portland, OR (Dr Tolosa); University of North Carolina at Chapel Hill, Chapel Hill, NC (Dr Thorp); University of Pittsburgh, Pittsburgh, PA (Dr Caritis); Medical University of South Carolina, Charleston, SC (Dr Van Dorsten); and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Bethesda, MD (Dr Spong).

Received July 28, 2012; revised Sept. 11, 2012; accepted Sept. 12, 2012.

The project described was supported by grant numbers HD21410, UL1 RR024153, UL1 TR000005, HD27869, HD27915, HD27917, HD34116, HD34208, 5UL1RR025764, HD36801, HD40500, HD40512, HD40544, M01 RR00080, UL1 RR024989 (National Center for Research Resources [NCRR]), HD40545, HD40560, HD40485, HD53097, and HD53118 from the NICHD.

ClinicalTrials.gov number, NCT00439374.

The authors report no conflict of interest.

This paper does not necessarily represent the official views of the NCRR, NICHD, or National Institutes of Health.

Other members of the NICHD MFMU Network are listed in the Acknowledgments.

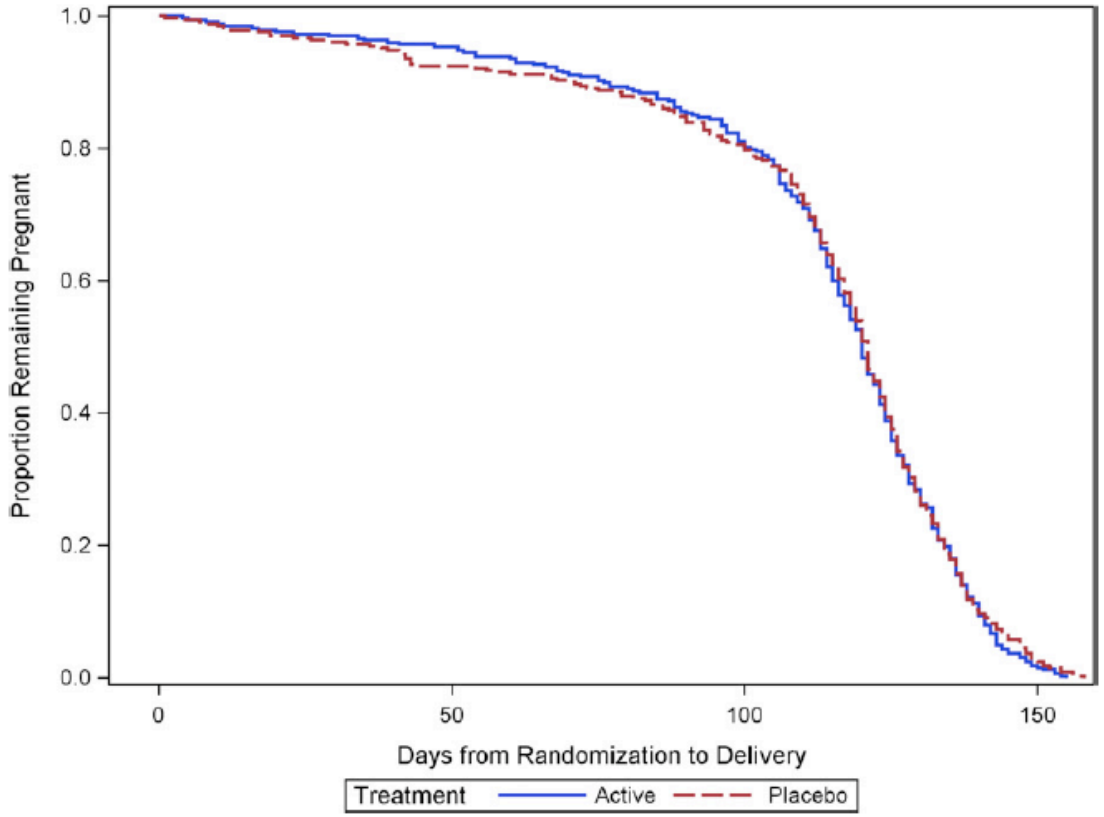
Presented at the 32nd annual meeting of the Society for Maternal-Fetal Medicine, Dallas, TX, Feb. 6-11, 2012.

Reprints not available from the authors.

 • http://dx.doi.org/10.1016/j.ajog.2012.09.013

For Editors' Commentary, see Contents

FIGURE 2
Survival curve illustrating proportion of participants remaining pregnant after randomization



Grobman. 17 alpha-hydroxyprogesterone caproate for nulliparas with cervical length <30 mm. Am J Obstet Gynecol 2012.

Grobman et al. AJOG. 2012

Role of progestogen in pregnancy AFTER TOCOLYSIS?

Role of progestogen in pregnancy AFTER TOCOLYSIS? NO

Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: A randomized controlled trial

Patrick Rozenberg, MD; Aurelia Chauveaud, MD; Philippe Deruelle, MD, PhD; Marianne Capelle, MD; Norbert Winer, MD, PhD; Raoul Desbrière, MD; Frank Perrotin, MD, PhD; Caroline Bohec, MD; Laure Connan, MD; Christophe Vayssière, MD, PhD; Bruno Langer, MD, PhD; Aymeric Mantel, MD; Shohreh Azimi; Raphael Porcher, MD, PhD; Elie Azria, MD, PhD; for the Groupe De Recherche En Obstétrique et Gynécologie

OBJECTIVE: The objective of the study was to evaluate the use of 17 alpha-hydroxyprogesterone caproate (17P) to reduce preterm delivery.

STUDY DESIGN: This open-label, multicenter, randomized controlled trial included women with singleton pregnancies admitted at 24-31 weeks' gestation and cervical length less than 25 mm for preterm labor successfully arrested by tocolytic treatment. Randomization assigned them to receive (or not) 500 mg of intramuscular 17P after tocolysis ended, repeated semiweekly until 36 weeks or preterm delivery. The primary outcome was the time from randomization to delivery.

RESULTS: Outcome data were available for 184 of 188 women randomized. The 17P and control groups (similar for most baseline characteristics) did not differ significantly for median [interquartile range] time to delivery (64 [42–79] and 67 [46–83] days, respectively) or rates of delivery before 37, 34, or 32 weeks of gestation or adverse perinatal outcomes.

CONCLUSION: Semiweekly injections of 17P did not prolong pregnancy significantly in women with tocolysis-arrested preterm labor.

Key words: cervical length, preterm delivery, preterm labor, 17 alpha-hydroxyprogesterone caproate, ultrasonography

Cite this article as: Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol 2012;206:206.e1-9.

Preterm birth, before 37 completed weeks of gestation, is responsible for most of the neonatal morbidity and mortality in developed countries and is a leading cause of long-term disability.[1,2] Rates in Europe generally range from 5% to 9%.[1] They have been rising in most industrialized countries, increasing in the United States from 9.5% in 1981 to 12.7% in 2005.[3,4] Although understanding of the risk factors and mechanisms related to preterm labor continues to advance,[5] lack of knowledge about its precise pathophysiology makes it difficult to improve these results. Tocolytic drugs can attempt to treat only the symptoms of preterm labor. Although all current tocolytic agents are superior to placebo at delaying delivery for both 48 hours and 7 days,[6] maintenance tocolytic therapy after successful treatment of an acute episode of preterm labor does not reduce the incidence of recurrent preterm labor or preterm delivery and does not improve perinatal outcome.[7]

Because of progesterone's role in maintaining pregnancy,[8-14] recent randomized trials have compared it with placebo in different groups at high risk for preterm delivery. Encouraging data suggest that prophylactic treatment with progesterone significantly reduces the rate of preterm delivery in women with a documented history of spontaneous preterm delivery[15,16] and in asymptomatic women with a short cervix measured at midgestation by ultrasound.[17]

Nevertheless, considerable uncertainty still surrounds the actual mechanism of

From the Departments of Obstetrics and Gynecology, Hôpital Poissy-Saint Germain, Versailles-St Quentin University, Poissy (Dr Rozenberg); Hôpital Antoine Béclère, Assistance Publique-Hôpitaux de Paris, Clamart (Dr Chauveaud); Hôpital Jeanne de Flandre, Lille (Dr Deruelle); Hôpitals de La Conception (Dr Capelle) and Nord (Dr Desbrière), Marseille; Hôpital Mère-Enfant, Nantes (Dr Winer); Hôpital Bretonneau, Tours (Dr Perrotin); Hôpital Morvan, Brest (Dr Bohec); Hôpital Paul de Viguier, Toulouse (Dr Connan); CMCO, Schiltigheim (Dr Vayssière); Hôpital Hautepierre, Strasbourg (Dr Langer); Hertford British Hospital, Levallois-Perret (Dr Mantel); and Hôpital Cochin–Port Royal Saint Vincent de Paul, Assistance Publique-Hôpitaux de Paris, Paris (Dr Azria); and the Department of Clinical Research Ile-de-France, Hôpital Saint-Louis, Assistance Publique–Hôpitaux de Paris, Paris (Ms Azimi), and the Department of Biostatistics, Hôpital Saint-Louis, Paris Diderot University, and Institut National de la Santé et de la Recherche Médicale (Dr Porcher), Paris, France.

Received Oct. 21, 2011; revised Dec. 9, 2011; accepted Dec. 21, 2011.

This trial was supported by a research grant from the Département à la Recherche Clinique Ile-de-France, Assistance Publique–Hôpitaux de Paris, which also sponsored the study (PHRC AOM 04038).

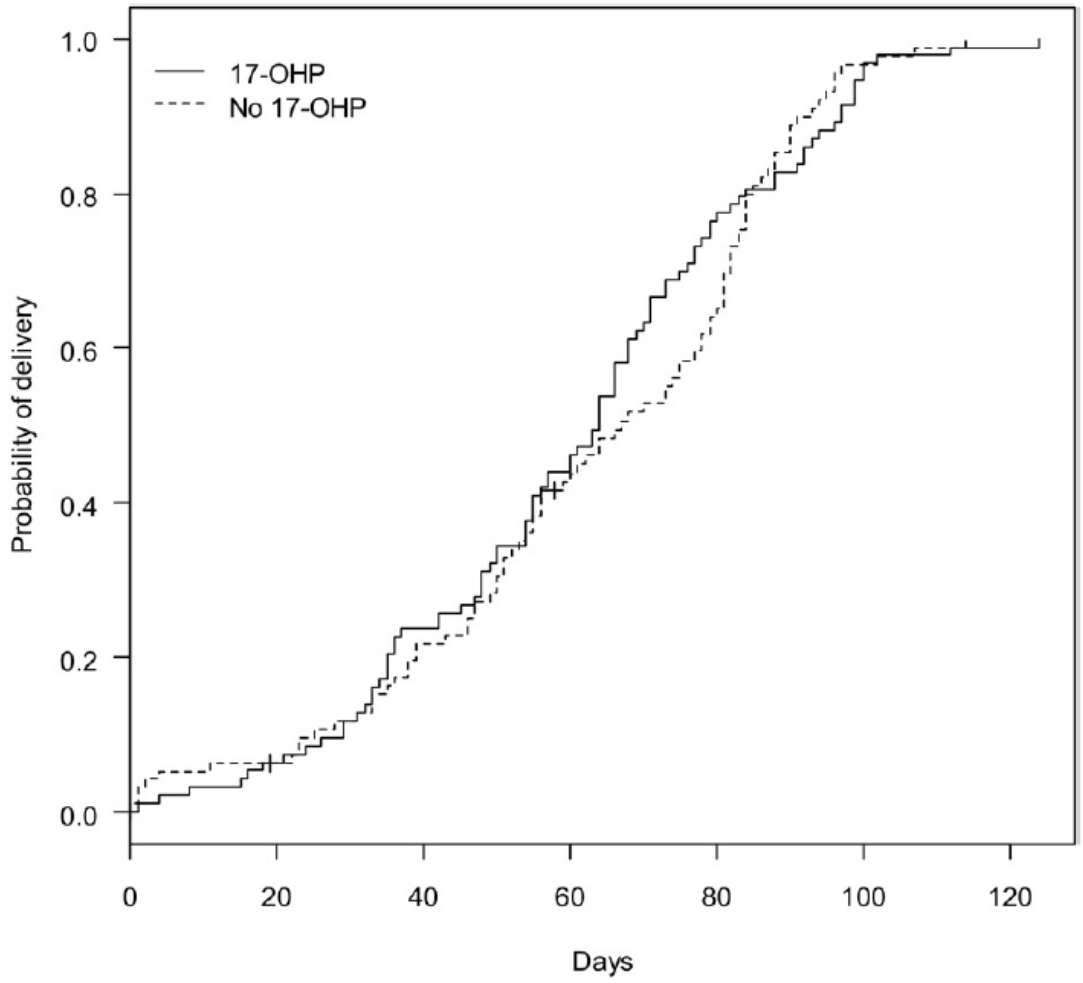
The authors report no conflicts of interest.

Presented orally at the 32nd annual meeting of the Society for Maternal-Fetal Medicine, Dallas, TX, Feb. 6-11, 2012.

The racing flag logo above indicates that this article was rushed to press for the benefit of the scientific community.

Reprints: Patrick Rozenberg, MD, Centre Hospitalier Poissy-Saint-Germain, Rue du Champ Gaillard, 78303 Poissy Cedex, France. prozenberg@chi-poissy-st-germain.fr.

0002-9378/$36.00 • © 2012 Published by Mosby, Inc. • doi: 10.1016/j.ajog.2011.12.026



Rozenberg. Prevention of preterm delivery after tocolysis in preterm labor. Am J Obstet Gynecol 2012.

Rozenberg P et al. AJOG. 2012

UTSouthwestern Medical Center

Role of progestogen in pregnancy, 2012

SMFM Clinical Guideline www.AJOG.org

Progesterone and preterm birth prevention: translating clinical trials data into clinical practice

Society for Maternal-Fetal Medicine Publications Committee, with the assistance of Vincenzo Berghella, MD

OBJECTIVE: We sought to provide evidence-based guidelines for using progestogens for the prevention of preterm birth (PTB).

METHODS: Relevant documents, in particular randomized trials, were identified using PubMed (US National Library of Medicine, 1983 through February 2012) publications, written in English, which evaluate the effectiveness of progestogens for prevention of PTB. Progestogens evaluated were, in particular, vaginal progesterone and 17-alpha-hydroxy-progesterone caproate. Additionally, the Cochrane Library, organizational guidelines, and studies identified through review of the above were utilized to identify relevant articles. Data were evaluated according to population studied, with separate analyses for singleton vs multiple gestations, prior PTB, or short transvaginal ultrasound cervical length (CL), and combinations of these factors. Consistent with US Preventive Task Force suggestions, references were evaluated for quality based on the highest level of evidence, and recommendations were graded.

RESULTS AND RECOMMENDATIONS: Summary of randomized studies indicates that in women with singleton gestations, no prior PTB, and short CL ≤20 mm at ≤24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in PTB and perinatal morbidity and mortality, and can be offered in these cases. The issue of universal CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners, following strict guidelines. In singleton gestations with prior PTB 20-36 6/7 weeks, 17-alpha-hydroxy-progesterone caproate 250 mg intramuscularly weekly, preferably starting at 16-20 weeks until 36 weeks, is recommended. In these women with prior PTB, if the transvaginal ultrasound CL shortens to <25 mm at <24 weeks, cervical cerclage may be offered. Progestogens have not been associated with prevention of PTB in women who have in the current pregnancy multiple gestations, preterm labor, or preterm premature rupture of membranes. There is insufficient evidence to recommend the use of progestogens in women with any of these risk factors, with or without a short CL.

Key words: 17-alpha-hydroxy-progesterone caproate, cervical length, preterm birth, prior preterm birth, progestogens, vaginal progesterone

Introduction

Progesterone was isolated and characterized in 1934, and its role in myometrial quiescence was first reported in 1954.[1,2] From 2003 through 2011, several randomized trials evaluating the effect of either 17-alpha-hydroxy-progesterone caproate (17P) given intramuscularly (IM) or natural progesterone given vaginally or orally for prevention of preterm birth (PTB) have been published. The term "progestogens" includes both vaginal progesterone and 17P.

Given this large amount of new important information, the scope of this article is to review the level-1 evidence (randomized controlled trials [RCTs] and metaanalyses of RCTs) evaluating the role of progestogens in the prevention of PTB, and to provide clinicians with current recommendations for their use in possible clinical scenarios. Other publications have not addressed the totality of this new information.[3-5]

As 17P and vaginal progesterone may vary in their effect,[6,7] they will be addressed separately. The effects of interventions for reduction of PTB often vary by the population studied, and in particular by major risk factor categories for PTB. Major differences exist when analyzing effects of other interventions by number of fetuses (ie, singleton vs multiple gestations), prior PTB (vs not), and short cervical length (CL) on transvaginal ultrasound (TVU) (vs not).[8] Therefore data will be analyzed according to these major categories of risk.

What are the mechanism of action and safety data of progestogens? (Levels II and III)

The mechanisms of action and safety of progestogens are not the purpose of this review, and are discussed only briefly. While the exact mechanism of action of progestogens in preventing PTB is unknown, several possibilities have been proposed (Table 1).[9-17] In general, the evidence seems to favor 2 mechanisms: an antiinflammatory effect that counteracts the inflammatory process leading to PTB, and a local increase in progesterone in gestational tissues that counteracts the functional decrease in progesterone leading to PTB (Table 1).[9-17]

Regarding safety, several studies failed to detect any long-term effect from the intrauterine exposure of the fetus to pharmacologic progestogens, even when given in the first trimester.[18] Follow-up, at a mean of 4 years, of 278 children randomized in the largest RCT evaluating 17P for prevention of recurrent PTB revealed no differences in physical examination, health status, or performance (motor, problem solving, personal-social) compared to placebo.[19]

From the Society for Maternal-Fetal Medicine Publications Committee with the assistance of Vincenzo Berghella, MD, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA.

Received March 12, 2012; accepted March 13, 2012.

The authors report no conflict of interest.

Reprints not available from the authors.

0002-9378/free

doi: 10.1016/j.ajog.2012.03.010

TABLE 3

Current Society for Maternal-Fetal Medicine recommendations regarding use of progestogens for prevention of preterm birth

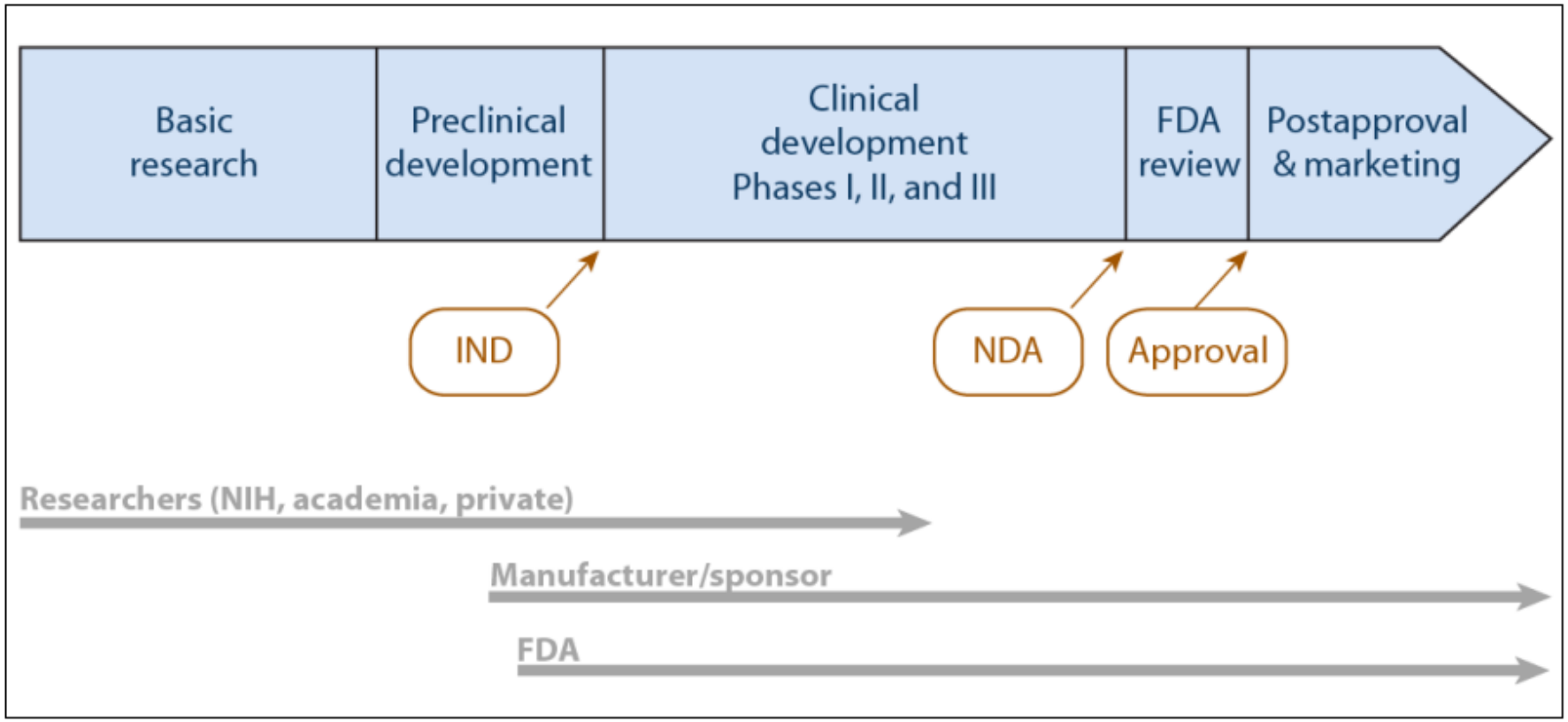
Population	Recommendation regarding use of progestogens
Asymptomatic	
Singletons without prior SPTB and unknown or normal TVU CL	No evidence of effectiveness
Singletons with prior SPTB	17P 250 mg IM weekly from 16-20 wk until 36 wk
Singletons without prior SPTB but CL ≤20 mm at ≤24 wk	Vaginal progesterone 90-mg gel or 200-mg suppository daily from diagnosis of short CL until 36 wk
Multiple gestations	No evidence of effectiveness
Symptomatic	
PTL	No evidence of effectiveness
PPROM	No evidence of effectiveness

17P, 17-alpha-hydroxy-progesterone caproate; *CL*, cervical length; *IM*, intramuscularly; *PPROM*, preterm premature rupture of membranes; *PTL*, preterm labor; *SPTB*, spontaneous preterm birth; *TVU*, transvaginal ultrasound.

SMFM. Progesterone and preterm birth prevention. Am J Obstet Gynecol 2012.

SMFM Publications Committee. AJOG. 2012

US FDA Approval Pathway

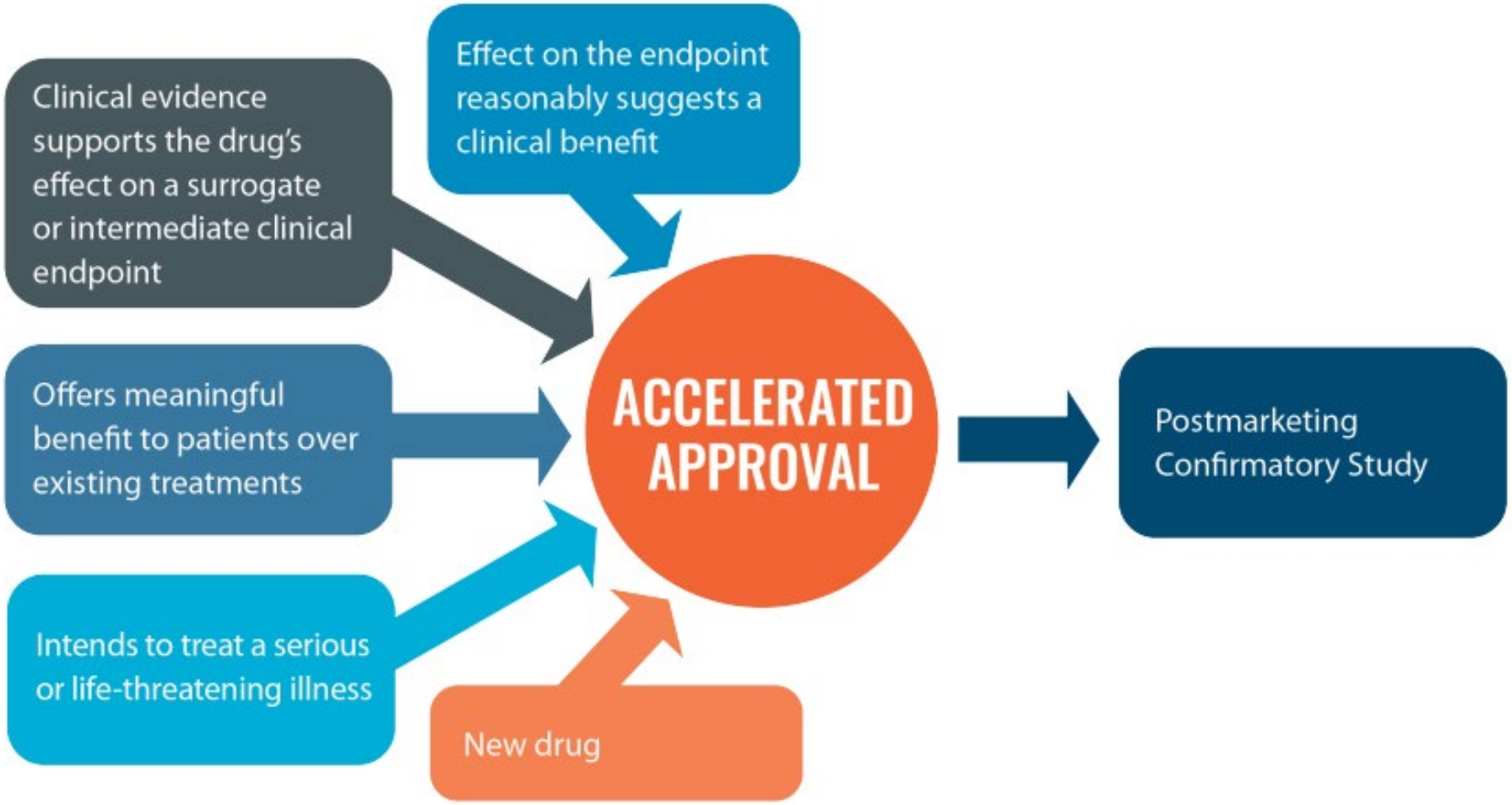


Source: Created by CRS.

Note: FDA = Food and Drug Administration. IND = investigational new drug application. NDA = new drug application. NIH = National Institutes of Health.

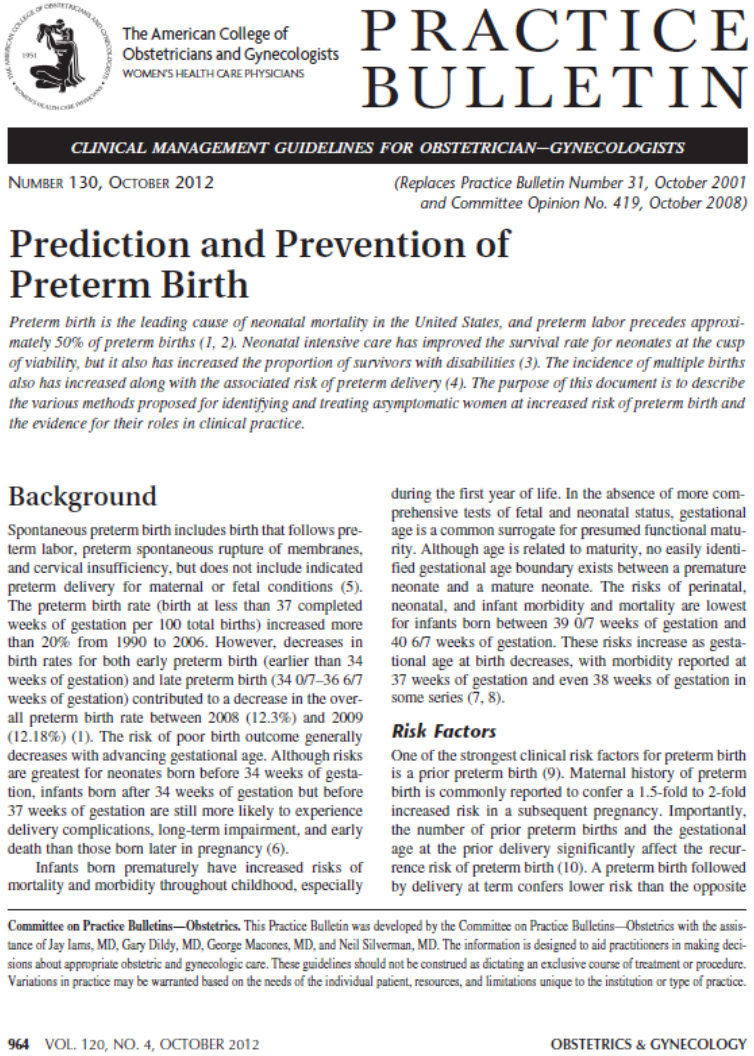
From Congressional Research Service Report, 2018

Accelerated Approval Pathway



From FDA'S Accelerated Approval Pathway: A rare disease perspective, 2021

Role of progestogen in pregnancy, 2012



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN—GYNECOLOGISTS

NUMBER 130, OCTOBER 2012

(Replaces Practice Bulletin Number 31, October 2001 and Committee Opinion No. 419, October 2008)

Prediction and Prevention of Preterm Birth

Preterm birth is the leading cause of neonatal mortality in the United States, and preterm labor precedes approximately 50% of preterm births (1, 2). Neonatal intensive care has improved the survival rate for neonates at the cusp of viability, but it also has increased the proportion of survivors with disabilities (3). The incidence of multiple births also has increased along with the associated risk of preterm delivery (4). The purpose of this document is to describe the various methods proposed for identifying and treating asymptomatic women at increased risk of preterm birth and the evidence for their roles in clinical practice.

Background

Spontaneous preterm birth includes birth that follows preterm labor, preterm spontaneous rupture of membranes, and cervical insufficiency, but does not include indicated preterm delivery for maternal or fetal conditions (5). The preterm birth rate (birth at less than 37 completed weeks of gestation per 100 total births) increased more than 20% from 1990 to 2006. However, decreases in birth rates for both early preterm birth (earlier than 34 weeks of gestation) and late preterm birth (34 0/7–36 6/7 weeks of gestation) contributed to a decrease in the overall preterm birth rate between 2008 (12.3%) and 2009 (12.18%) (1). The risk of poor birth outcome generally decreases with advancing gestational age. Although risks are greatest for neonates born before 34 weeks of gestation, infants born after 34 weeks of gestation but before 37 weeks of gestation are still more likely to experience delivery complications, long-term impairment, and early death than those born later in pregnancy (6).

Infants born prematurely have increased risks of mortality and morbidity throughout childhood, especially during the first year of life. In the absence of more comprehensive tests of fetal and neonatal status, gestational age is a common surrogate for presumed functional maturity. Although age is related to maturity, no easily identified gestational age boundary exists between a premature neonate and a mature neonate. The risks of perinatal, neonatal, and infant morbidity and mortality are lowest for infants born between 39 0/7 weeks of gestation and 40 6/7 weeks of gestation. These risks increase as gestational age at birth decreases, with morbidity reported at 37 weeks of gestation and even 38 weeks of gestation in some series (7, 8).

Risk Factors

One of the strongest clinical risk factors for preterm birth is a prior preterm birth (9). Maternal history of preterm birth is commonly reported to confer a 1.5-fold to 2-fold increased risk in a subsequent pregnancy. Importantly, the number of prior preterm births and the gestational age at the prior delivery significantly affect the recurrence risk of preterm birth (10). A preterm birth followed by delivery at term confers lower risk than the opposite

Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the Committee on Practice Bulletins—Obstetrics with the assistance of Jay Iams, MD, Gary Dildy, MD, George Macones, MD, and Neil Silverman, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

964 VOL. 120, NO. 4, OCTOBER 2012 OBSTETRICS & GYNECOLOGY

ACOG Practice Bulletin No 130. 2012

Role of progestogen in pregnancy

Original retail price: $1500 per 250 mg injectable dose.

($30,000+ per pregnancy)

Role of progestogen in pregnancy

Original retail price: $1500 per 250 mg injectable dose.

($30,000+ per pregnancy)

In Dallas, a 250 mg injectable dose of compounded 17 alpha hydroxyprogesterone caproate currently costs approximately $18 in 2011

($360 per pregnancy)

Role of progestogen in pregnancy

Current Commentary

Unjustified Increase in Cost of Care Resulting From U.S. Food and Drug Administration Approval of Makena (17α-Hydroxyprogesterone Caproate)

Arnold W. Cohen, MD, Joshua A. Copel, MD, George A. Macones, MD, M. Kathryn Menard, MD, MPH, Laura Riley, MD, and George R. Saade, MD

U.S. Food and Drug Administration (FDA) approval of 17α-hydroxyprogesterone caproate for the indication of decreasing the risk of preterm delivery in those high-risk patients who previously had spontaneous preterm birth has come at considerable cost to the health care system. Weekly injections provided by compounding pharmacies starting at 16–20 weeks of gestation and continuing until 36 weeks currently cost the health care system $200 to $300 per pregnancy. This cost is significantly less than the costs associated with delivering and caring for preterm children. Makena, by KV Pharmaceutical, the same 17α-hydroxyprogesterone caproate product, is priced at $1,500 per injection, or a projected cost of $30,000 per pregnancy. With approximately 132,000 pregnancies being eligible for treatment annually, this increase in cost of 75–150 times what previously had been paid far exceeds the benefits derived from the FDA-approved Makena when compared with previously available compounded versions of 17α-hydroxyprogesterone caproate. This increased health care cost is not justified at this time. The price barrier to access imposed by KV Pharmaceutical actually could result in an increase in preterm deliveries over current rates. Actions are needed by the FDA, national societies, and the manufacturer to ensure that all high-risk patients continue to get the needed therapy to reduce the number of preterm births.

(Obstet Gynecol 2011;117:1408–12)
DOI: 10.1097/AOG.0b013e31821c2d75

See related editorial on page 1263.

From the Albert Einstein Medical Center, Philadelphia, Pennsylvania; the Yale University School of Medicine, New Haven, Connecticut; the Washington University School of Medicine, St. Louis, Missouri; the University of North Carolina School of Medicine, Chapel Hill, North Carolina; Massachusetts General Hospital, Boston, Massachusetts; and the University of Texas Medical Branch, Galveston, Texas.

Corresponding author: M. Kathryn Menard, MD, MPH, CB# 7516, 3010 Old Clinic Bldg., Chapel Hill, NC 27599-7516, 919-966-1601; e-mail: kmenard@med.unc.edu.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/11

Obstetricians have been searching for the key to preventing preterm birth for more than half a century. Our quest for a "cure" for prematurity has led to many therapies, including alcohol, ritodrine (U.S. Food and Drug Administration [FDA]-approved, later withdrawn from the market), terbutaline, nifedipine, indomethacin, magnesium sulfate, and atosiban. At best, each delays delivery for 24–48 hours, just enough time to give women at risk of preterm delivery corticosteroids, an intervention that has been shown to enhance fetal pulmonary maturation and decrease the risk of respiratory distress syndrome, severe intraventricular hemorrhage, necrotizing enterocolitis, and death.[1]

In 1975, in a small trial, Johnson found that weekly injections of 17α-hydroxyprogesterone caproate improved the outcomes of selected high-risk pregnancies.[2] In 1956, the FDA had approved 17α-hydroxyprogesterone caproate under the trade name Delalutin for use in pregnant women. The manufacturer withdrew Delalutin from the market in 2000 for reasons unrelated to safety.[3] Compounded progesterone therapy during pregnancy then was used only rarely.

In 2003, Meis published the results of a National Institutes of Health–sponsored double-blind, randomized, placebo-controlled study testing the efficacy of 17α-hydroxyprogesterone caproate for the prevention of recurrent premature birth.[4] In this study, the incidence of recurrent premature delivery at less than

Editorials

Deus ex Makena?

Robert M. Silver, MD

F. Gary Cunningham, MD

See related article on page 1408.

Dr. Silver is from the University of Utah Health Sciences Center, Department of Obstetrics and Gynecology, Salt Lake City, Utah; e-mail: bob.silver@hsc.utah.edu. Dr. Cunningham is from the University of Texas Southwestern Medical Center at Dallas, Department of Obstetrics and Gynecology, Dallas, Texas; e-mail: gary.cunningham@utsouthwestern.edu.

Financial Disclosure
The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/11

The Latin phrase *deus ex machina* refers to a practice revived during the Shakespearean era in which the plot of a tragic play was augmented by a device (*machina*) that introduced a god (*deus*) onstage to resolve a difficult situation or predicament. Given the recent "predicament" surrounding the release of Makena for preterm labor prevention, we now explore whether this drug is indeed the "divine" intervention that provides us with a solution–hence our title, "*Deus ex* Makena?" Most certainly, the recent U.S. Food and Drug Administration (FDA) approval for KV Pharmaceutical to market 17α-hydroxyprogesterone caproate was much heralded by the obstetric community. Despite decades of research, no medication has held such promise in the prevention of some cases of preterm birth. The initial excitement was dampened quickly when the company announced that the wholesale price for Makena would be nearly $1,500 for each weekly injection. This compares with about $10 to $20 for 7 days of treatment with progesterone vaginal suppositories. Annual costs for 17α-hydroxyprogesterone caproate to prevent preterm labor in eligible women in this country are estimated to exceed $3 billion, without including any added costs for drug administration. Timely and appropriate umbrage similar to that expressed by Cohen et al in this issue[1] also has come from the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the Society for Maternal-Fetal Medicine, and economists, ethicists, politicians, and other knowledgeable sources.[2]

The current renaissance of interest in the prevention of preterm labor with progesterone followed publication in 2003 of the trial by the Maternal-Fetal Medicine Units Network.[3] This study included, for the most part, women at very high risk for recurrent preterm birth who were assigned randomly at midpregnancy to receive weekly injections of either intramuscular 17α-hydroxyprogesterone caproate in castor oil or placebo. Women in the 17α-hydroxyprogesterone caproate–treated group had significantly fewer preterm births. However, when major neonatal morbidities were compared between the two cohorts, there were no meaningful differences in the frequency of respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, or retinopathy. Two subsequent Maternal-Fetal Medicine Units Network studies done to assess the efficacy of 17α-hydroxyprogesterone caproate to prevent preterm delivery in women with twin or triplet gestations report no benefits for pregnancy prolongation.[4,5]

In addition to the studies cited above, there have been a number of other well-designed clinical trials carried out over the past decade to assess the efficacy of preterm labor prevention with 17α-hydroxyprogesterone caproate as well as other progestational compounds. In a Brazilian study, women at high risk for preterm labor were assigned randomly to daily treatment with vaginal suppositories containing either placebo or 100 mg of progesterone.[6] These investigators describe results with progesterone-containing suppositories similar to those from the 17α-hydroxyprogesterone caproate trial, in that the risk for preterm delivery was decreased significantly in the progesterone-

Cohen et al. Obstet Gynecol. 2011

Silver, Cunningham. Obstet Gynecol. 2012

Local experiences with progestogens

At Parkland Health in 2012…

- Weekly 17 alpha hydroxyprogesterone caproate beginning at 16 – $20^{6/7}$ weeks for women with prior spontaneous preterm birth
- 250 mg weekly injection
- Given until 36 completed weeks (i.e. $37^{0/7}$)
- **Compounded therapy versus Commercial product???**

At Parkland Health

EAGLE
ANALYTICAL SERVICES
A PCCA COMPANY

LABORATORY REPORT

4/25/2012

Joe Park
Dougherty's Pharmacy
515 Preston Royal Village
Dallas, TX 75230
Tel: (214) 363-4318
Fax: (214) 739-0238

Client #: E12417
Sample: **Hydroxyprogesterone Caproate Sesame 250mg/mL**
Lot #: YU-YH-DYJD@38
Sample ID #: 259361
Date Rec'd: 4/18/2012

LABORATORY TEST RESULTS

Microbiological Tests:	***Date***	***Measured***	***Result***
Bacterial Endotoxin USP <85>	--		
Sterility USP <71>	Day 7 (Neg.)		
Rapid ScanRDI Microbial Detection	--		

Chemical Tests:	***Date***	***Reported***	***Measured***	***Potency***
Hydroxyprogesterone Caproate	4/24/2012	250 mg/mL	248 mg/mL	99.2 %

Notes:

USP <71> Sterility Test is a 14 day test using the membrane filtration procedure. Test for BACTERIA, MOLDS, YEAST AND FUNGI with two media at separate temperatures. Test read on days 3, and 7 are not final until the full 14 day test is complete.

USP <795> states: "...compound preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of an active ingredient...". Potency is determinations follow USP <621> HPLC, USP<851> Spectrophotometry, and specific monograph testing procedures.

Respectfully submitted,
EAGLE ANALYTICAL SERVICES LTD.

William J. Zolner, Ph.D., President

9881 South Wilcrest Drive, Houston, TX 77099 832-295-1276 281-754-4700 (fax)

At Parkland Health

EAGLE
ANALYTICAL SERVICES
A PCCA COMPANY

LABORATORY REPORT

4/25/2012

Joe Park
Dougherty's Pharmacy
515 Preston Royal Village
Dallas, TX 75230
Tel: (214) 363-4318
Fax: (214) 739-0238

Client #: E12417
Sample: **Hydroxyprogesterone Caproate Sesame**
250mg/mL
Lot #: YU-YH-DYJD@38
Sample ID #: 259361
Date Rec'd: 4/18/2012

LABORATORY TEST RESULTS

Microbiological Tests:	***Date***	***Measured***	***Result***
Bacterial Endotoxin USP <85>	--		
Sterility USP <71>	Day 7 (Neg.)		
Rapid ScanRDI Microbial Detection	--		

Chemical Tests:	***Date***	***Reported***	***Measured***	***Potency***
Hydroxyprogesterone Caproate	4/24/2012	250 mg/mL	248 mg/mL	99.2 %

Notes:

USP <71> Sterility Test is a 14 day test using the membrane filtration procedure. Test for BACTERIA, MOLDS, YEAST AND FUNGI with two media at separate temperatures. Test read on days 3, and 7 are not final until the full 14 day test is complete.

USP <795> states: "...compound preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of an active ingredient...". Potency is determinations follow USP <621> HPLC, USP<851> Spectrophotometry, and specific monograph testing procedures.

Respectfully submitted,
EAGLE ANALYTICAL SERVICES LTD.

William J. Zolner, Ph.D., President

9881 South Wilcrest Drive, Houston, TX 77099 832-295-1276 281-754-4700 (fax)

At Parkland Health

EAGLE
ANALYTICAL SERVICES
A PCCA COMPANY

LABORATORY REPORT

4/25/2012

Joe Park
Dougherty's Pharmacy
515 Preston Royal Village
Dallas, TX 75230
Tel: (214) 363-4318
Fax: (214) 739-0238

Client #: E12417
Sample: **Hydroxyprogesterone Caproate Sesame**
250mg/mL
Lot #: YU-YH-DYJD@38
Sample ID #: 259361
Date Rec'd: 4/18/2012

LABORATORY TEST RESULTS

Microbiological Tests:	***Date***	***Measured***	***Result***
Bacterial Endotoxin USP <85>	--		
Sterility USP <71>	Day 7 (Neg.)		
Rapid ScanRDI Microbial Detection	--		

Chemical Tests:	***Date***	***Reported***	***Measured***	***Potency***
Hydroxyprogesterone Caproate	4/24/2012	250 mg/mL	248 mg/mL	99.2 %

Notes:

USP <71> Sterility Test is a 14 day test using the membrane filtration procedure. Test for BACTERIA, MOLDS, YEAST AND FUNGI with two media at separate temperatures. Test read on days 3, and 7 are not final until the full 14 day test is complete.

USP <795> states: "...compound preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of an active ingredient...". Potency is determinations follow USP <621> HPLC, USP<851> Spectrophotometry, and specific monograph testing procedures.

Respectfully submitted,
EAGLE ANALYTICAL SERVICES LTD.

William J. Zolner, Ph.D., President

9881 South Wilcrest Drive, Houston, TX 77099 832-295-1276 281-754-4700 (fax)

CDC Home

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

Recommend Tweet Share

Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy — United States, 2012

Weekly
October 19, 2012 / 61(41);839-842

On October 12, 2012, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

On September 18, 2012, the Tennessee Department of Health was alerted by a clinician regarding a patient with culture-confirmed *Aspergillus fumigatus* meningitis diagnosed 46 days after epidural steroid injection at a Tennessee ambulatory surgical center. By September 27, the initial investigation, carried out by the Tennessee Department of Health in collaboration with CDC and the North Carolina Department of Health and Human Services, had identified an additional eight patients with clinically diagnosed, culture-negative meningitis: seven in Tennessee and one in North Carolina. All nine patients had received epidural steroid injection with preservative-free methylprednisolone acetate solution (MPA), compounded at New England Compounding Center (NECC) in Framingham, Massachusetts. All nine patients had received one or more injections from three lots of MPA (lot numbers 05212012@68; 06292012@26; and 08102012@51). As of October 10, a multistate investigation led by CDC in collaboration with state and local health departments and the Food and Drug Administration (FDA) had identified 137 cases and 12 deaths associated with this outbreak in 10 states. Active case-finding efforts and extensive investigation into medications and medication lot numbers received by patients have confirmed that, as of October 10, no cases were associated with other lots of MPA, nor were any associated with other NECC products. This report describes the ongoing investigation by CDC and state and local health departments, and includes important recommendations for physicians and patients.

NECC was informed of the ongoing investigation on September 25 and provided invoice information indicating that approximately 17,500 vials of MPA (80 mg/ml) from these lots were packaged in 1ml, 2ml, and 5ml vials and distributed to 75 facilities in 23 states. These lots of MPA were used to treat both peripheral joint and back pain. On September 26, NECC voluntarily recalled the three lots of MPA, followed by an expanded voluntary recall of all lots of MPA and all lots of sterile products intended for intrathecal injection on October 3. This was followed by a voluntary recall of all remaining products on October 6.

At Parkland Health

EAGLE
ANALYTICAL SERVICES
A PCCA COMPANY

LABORATORY REPORT

4/25/2012

Joe Park
Dougherty's Pharmacy
515 Preston Royal Village
Dallas, TX 75230
Tel: (214) 363-4318
Fax: (214) 739-0238

Client #: E12417
Sample: **Hydroxyprogesterone Caproate Sesame 250mg/mL**
Lot #: YU-YH-DYJD@38
Sample ID #: 259361
Date Rec'd: 4/18/2012

LABORATORY TEST RESULTS

Microbiological Tests:	***Date***	***Measured***	***Result***
Bacterial Endotoxin USP <85>	--		
Sterility USP <71>	Day 7 (Neg.)		
Rapid ScanRDI Microbial Detection	--		

Chemical Tests:	***Date***	***Reported***	***Measured***	***Potency***
Hydroxyprogesterone Caproate	4/24/2012	250 mg/mL	248 mg/mL	99.2 %

Notes:

USP <71> Sterility Test is a 14 day test using the membrane filtration procedure. Test for BACTERIA, MOLDS, YEAST AND FUNGI with two media at separate temperatures. Test read on days 3, and 7 are not final until the full 14 day test is complete.

USP <795> states: "...compound preparations are to be prepared to ensure that each preparation shall contain not less than 90% and not more than 110% of the theoretically calculated and labeled quantity of an active ingredient...". Potency is determinations follow USP <621> HPLC, USP<851> Spectrophotometry, and specific monograph testing procedures.

Respectfully submitted,
EAGLE ANALYTICAL SERVICES LTD.

William J. Zolner, Ph.D., President

9881 South Wilcrest Drive, Houston, TX 77099 832-295-1276 281-754-4700 (fax)

CDC Home

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

Recommend Tweet Share

Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy — United States, 2012

Weekly
October 19, 2012 / 61(41);839-842

On October 12, 2012, this report was posted as an MMWR *Early Release on the* MMWR *website (http://www.cdc.gov/mmwr).*

On September 18, 2012, the Tennessee Department of Health was alerted by a clinician regarding a patient with culture-confirmed *Aspergillus fumigatus* meningitis diagnosed 46 days after epidural steroid injection at a Tennessee ambulatory surgical center. By September 27, the initial investigation, carried out by the Tennessee Department of Health in collaboration with CDC and the North Carolina Department of Health and Human Services, had identified an additional eight patients with clinically diagnosed, culture-negative meningitis: seven in Tennessee and one in North Carolina. All nine patients had received epidural steroid injection with preservative-free methylprednisolone acetate solution (MPA), compounded at New England Compounding Center (NECC) in Framingham, Massachusetts. All nine patients had received one or more injections from three lots of MPA (lot numbers 05212012@68; 06292012@26; and 08102012@51). As of October 10, a multistate investigation led by CDC in collaboration with state and local health departments and the Food and Drug Administration (FDA) had identified 137 cases and 12 deaths associated with this outbreak in 10 states. Active case-finding efforts and extensive investigation into medications and medication lot numbers received by patients have confirmed that, as of October 10, no cases were associated with other lots of MPA, nor were any associated with other NECC products. This report describes the ongoing investigation by CDC and state and local health departments, and includes important recommendations for physicians and patients.

NECC was informed of the ongoing investigation on September 25 and provided invoice information indicating that approximately 17,500 vials of MPA (80 mg/ml) from these lots were packaged in 1ml, 2ml, and 5ml vials and distributed to 75 facilities in 23 states. These lots of MPA were used to treat both peripheral joint and back pain. On September 26, NECC voluntarily recalled the three lots of MPA, followed by an expanded voluntary recall of all lots of MPA and all lots of sterile products intended for intrathecal injection on October 3. This was followed by a voluntary recall of all remaining products on October 6.

Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: A randomized controlled trial

Patrick Rozenberg, MD; Aurelia Chauveaud, MD; Philippe Deruelle, MD, PhD; Marianne Capelle, MD; Norbert Winer, MD, PhD; Raoul Desbrière, MD; Frank Perrotin, MD, PhD; Caroline Bohec, MD; Laure Connan, MD; Christophe Vayssière, MD, PhD; Bruno Langer, MD, PhD; Aymeric Mantel, MD; Shohreh Azimi; Raphael Porcher, MD, PhD; Elie Azria, MD, PhD; for the Groupe De Recherche En Obstétrique et Gynécologie

OBJECTIVE: The objective of the study was to evaluate the use of 17 alpha-hydroxyprogesterone caproate (17P) to reduce preterm delivery.

STUDY DESIGN: This open-label, multicenter, randomized controlled trial included women with singleton pregnancies admitted at 24-31 weeks' gestation and cervical length less than 25 mm for preterm labor successfully arrested by tocolytic treatment. Randomization assigned them to receive (or not) 500 mg of intramuscular 17P after tocolysis ended, repeated semiweekly until 36 weeks or preterm delivery. The primary outcome was the time from randomization to delivery.

RESULTS: Outcome data were available for 184 of 188 women randomized. The 17P and control groups (similar for most baseline characteristics) did not differ significantly for median [interquartile range] time to delivery (64 [42–79] and 67 [46–83] days, respectively) or rates of delivery before 37, 34, or 32 weeks of gestation or adverse perinatal outcomes.

CONCLUSION: Semiweekly injections of 17P did not prolong pregnancy significantly in women with tocolysis-arrested preterm labor.

Key words: cervical length, preterm delivery, preterm labor, 17 alpha-hydroxyprogesterone caproate, ultrasonography

Rozenberg P et al. AJOG. 2012

"Despite widespread clinical use, there are no reports that have described pharmacokinetics of 17-OHPC in singleton gestation, the plasma concentrations that are achieved during therapy for preterm birth prevention, and whether the medication is detectible in fetal blood"

"Despite widespread clinical use, there are no reports that have described pharmacokinetics of 17-OHPC in singleton gestation, the plasma concentrations that are achieved during therapy for preterm birth prevention, and whether the medication is detectible in fetal blood"

*-Caritis et al.**2012***

Pharmacology considerations

OBSTETRICS WORLD PREMATURITY DAY

Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation

Steve N. Caritis, MD; Shringi Sharma, PhD; Raman Venkataramanan, PhD; Gary D. Hankins, MD; Menachem Miodovnik, MD; Mary F. Hebert, PharmD; Jason G. Umans, MD, PhD; Thomas Benedetti, MD; Donald Mattison, MD; Anne Zajicek, MD, PharmD; Dawn Fischer, RN; Aimee Jackson, RNC, MSN; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetrical-Fetal Pharmacology Research Units Network

OBJECTIVE: The purpose of this study was to estimate pharmacokinetic parameters and to evaluate placental transport of 17-hydroxyprogesterone caproate (17-OHPC) in singleton gestation.

STUDY DESIGN: Sixty-one women who received weekly injections of 17-OHPC underwent 2 pharmacokinetic studies at 20 + 0 to 24 + 6 weeks' gestation (study 1) and 31 + 0 to 34 + 6 weeks' gestation (study 2); daily blood samples were obtained between injections. In 18 women, blood samples were obtained over a 28-day period beyond the last injection (extended study). Maternal and/or cord blood were obtained at delivery.

RESULTS: The half-life (median ± SD) of 17-OHPC was 16.2 ± 6 days. Concentrations of 17-OHPC were higher during study 2 than during study 1. Body mass index affected maternal 17-OHPC concentrations. Cord:maternal 17-OHPC concentration ratios averaged 0.2; 17-OHPC was detectible in cord plasma 44 days after the last maternal injection.

CONCLUSION: The apparent half-life of 17-OHPC is long, and pharmacokinetic parameters vary widely between subjects and are affected by maternal body mass index. The drug crosses the placental barrier.

Key words: cord blood, pharmacokinetics, placenta, preterm birth

Cite this article as: Caritis SN, Sharma S, Venkataramanan R, et al. Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation. Am J Obstet Gynecol 2012;207:398.e1-8.

Seventeen-hydroxyprogesterone caproate (17-OHPC) reduces preterm birth rates in women with a previous preterm birth[1] but has not proved effective in women with multifetal gestation[2,3] or an ultrasonically identified short cervix.[4] The American Congress of Obstetricians and Gynecologists in a 2009 Committee Opinion recommended that this therapy be offered to all women with a previous preterm birth[5] and that more research be done with the pharmacology of 17-OHPC and other progestin preparations. Despite widespread clinical use, there are no reports that have described pharmacokinetics of 17-OHPC in singleton gestation, the plasma concentrations that are achieved during therapy for preterm birth prevention, and whether the medication is detectible in fetal blood. In this multicenter Obstetrical-Fetal Pharmacology Research Units Network study, we evaluated the pharmacokinetics and placental transport of 17-OHPC in women with singleton gestation who were receiving 17-OHPC because of a previous preterm birth.

Materials and Methods

Study design

We recruited 61 women from 4 centers who were receiving or planned to receive 17-OHPC for the prevention of recurrent preterm birth based on a history of at least 1 previous spontaneous preterm (<37 weeks' gestation) birth. In keeping with clinical practice recommendations, all women who were receiving 17-OHPC began therapy between 16 0/7 and 20 6/7 weeks' gestation. Each subject agreed to participate in 2 pharmacokinetic studies lasting 7 days each. The first pharmacokinetic study (PK1) was scheduled to occur between 20 0/7 and 24 6/7 weeks' gestation after a minimum of 4 weekly

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine (Dr Caritis and Ms Fischer), and the Department of Pharmaceutical Sciences, School of Pharmacy (Drs Sharma and Venkataramanan), University of Pittsburgh, Pittsburgh, PA; the Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX (Dr Hankins and Ms Jackson); Washington Hospital Center, Washington, DC, and MedStar Health Research Institute, Hyattsville, MD (Drs Miodovnik and Umans); the Georgetown–Howard Universities Center for Clinical and Translational Science, Washington, DC (Dr Umans); the Departments of Pharmacy (Dr Hebert) and Obstetrics and Gynecology (Dr Benedetti), University of Washington School of Medicine, Seattle, WA; and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (Drs Mattison and Zajicek).

Received April 6, 2012; revised July 27, 2012; accepted Aug. 8, 2012.

Supported by the Obstetric Fetal Pharmacology Research Units Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development through cooperative agreements U10HD047905, U10HD047892, U10HD047892, and U10HD047892 with additional support by 1 UL1RR031975.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development or the National Institutes of Health.

The authors report no conflict of interest.

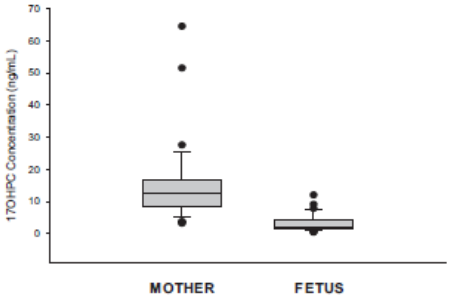
Reprints not available from the authors.

FIGURE 4

Relationship between maternal and cord blood concentrations of 17-OHPC

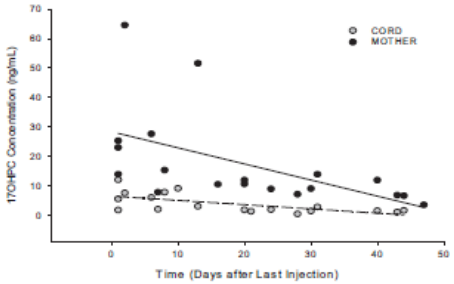
A

Plasma 17-OHPC concentrations in maternal and cord blood at time of delivery



B

Plasma 17-OHPC concentration in maternal and cord blood according to time from last injection of 17-OHPC



A, Box plot of 17-hydroxyprogesterone caproate concentration in maternal blood at the time of delivery and of cord blood. The *horizontal bar* is the median value; the *error bars* represent 25th (lower bar) and 75th (upper bar) percentiles. The *closed circles* outside the 25th and 75th percentiles represent outliers. **B,** Relationship between maternal and cord blood concentrations of 17-OHPC. The figure illustrates maternal blood and cord blood concentrations of 17-OHPC according to time from last maternal injection of 17-OHPC.

17-OHPC, 17-hydroxyprogesterone caproate.

Caritis. Pharmacology and placental transport of 17-OHPC. Am J Obstet Gynecol 2012.

Caritis SN et al. AJOG. 2012

Pharmacology and other effects…

OBSTETRICS WORLD PREMATURITY DAY

Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation

Steve N. Caritis, MD; Shringi Sharma, PhD; Raman Venkataramanan, PhD; Gary D. Hankins, MD; Menachem Miodovnik, MD; Mary F. Hebert, PharmD; Jason G. Umans, MD, PhD; Thomas Benedetti, MD; Donald Mattison, MD; Anne Zajicek, MD, PharmD; Dawn Fischer, RN; Aimee Jackson, RNC, MSN; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetrical-Fetal Pharmacology Research Units Network

OBJECTIVE: The purpose of this study was to estimate pharmacokinetic parameters and to evaluate placental transport of 17-hydroxyprogesterone caproate (17-OHPC) in singleton gestation.

STUDY DESIGN: Sixty-one women who received weekly injections of 17-OHPC underwent 2 pharmacokinetic studies at 20 + 0 to 24 + 6 weeks' gestation (study 1) and 31 + 0 to 34 + 6 weeks' gestation (study 2); daily blood samples were obtained between injections. In 18 women, blood samples were obtained over a 28-day period beyond the last injection (extended study). Maternal and/or cord blood were obtained at delivery.

RESULTS: The half-life (median ± SD) of 17-OHPC was 16.2 ± 6 days. Concentrations of 17-OHPC were higher during study 2 than during study 1. Body mass index affected maternal 17-OHPC concentrations. Cord:maternal 17-OHPC concentration ratios averaged 0.2; 17-OHPC was detectible in cord plasma 44 days after the last maternal injection.

CONCLUSION: The apparent half-life of 17-OHPC is long, and pharmacokinetic parameters vary widely between subjects and are affected by maternal body mass index. The drug crosses the placental barrier.

Key words: cord blood, pharmacokinetics, placenta, preterm birth

Cite this article as: Caritis SN, Sharma S, Venkataramanan R, et al. Pharmacology and placental transport of 17-hydroxyprogesterone caproate in singleton gestation. Am J Obstet Gynecol 2012;207:398.e1-8.

Seventeen-hydroxyprogesterone caproate (17-OHPC) reduces preterm birth rates in women with a previous preterm birth[1] but has not proved effective in women with multifetal gestation[2,3] or an ultrasonically identified short cervix.[4] The American Congress of Obstetricians and Gynecologists in a 2009 Committee Opinion recommended that this therapy be offered to all women with a previous preterm birth[5] and that more research be done with the pharmacology of 17-OHPC and other progestin preparations. Despite widespread clinical use, there are no reports that have described pharmacokinetics of 17-OHPC in singleton gestation, the plasma concentrations that are achieved during therapy for preterm birth prevention, and whether the medication is detectible in fetal blood. In this multicenter Obstetrical-Fetal Pharmacology Research Units Network study, we evaluated the pharmacokinetics and placental transport of 17-OHPC in women with singleton gestation who were receiving 17-OHPC because of a previous preterm birth.

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, School of Medicine (Dr Caritis and Ms Fischer), and the Department of Pharmaceutical Sciences, School of Pharmacy (Drs Sharma and Venkataramanan), University of Pittsburgh, Pittsburgh, PA; the Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX (Dr Hankins and Ms Jackson); Washington Hospital Center, Washington, DC, and MedStar Health Research Institute, Hyattsville, MD (Drs Miodovnik and Umans); the Georgetown–Howard Universities Center for Clinical and Translational Science, Washington, DC (Dr Umans); the Departments of Pharmacy (Dr Hebert) and Obstetrics and Gynecology (Dr Benedetti), University of Washington School of Medicine, Seattle, WA; and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD (Drs Mattison and Zajicek).

Received April 6, 2012; revised July 27, 2012; accepted Aug. 8, 2012.

Supported by the Obstetric Fetal Pharmacology Research Units Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development through cooperative agreements U10HD047905, U10HD047892, U10HD047892, and U10HD047892 with additional support by 1 UL1RR031975.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development or the National Institutes of Health.

The authors report no conflict of interest.

Reprints not available from the authors.

Materials and Methods

Study design

We recruited 61 women from 4 centers who were receiving or planned to receive 17-OHPC for the prevention of recurrent preterm birth based on a history of at least 1 previous spontaneous preterm (<37 weeks' gestation) birth. In keeping with clinical practice recommendations, all women who were receiving 17-OHPC began therapy between 16 0/7 and 20 6/7 weeks' gestation. Each subject agreed to participate in 2 pharmacokinetic studies lasting 7 days each. The first pharmacokinetic study (PK1) was scheduled to occur between 20 0/7 and 24 6/7 weeks' gestation after a minimum of 4 weekly

Caritis SN et al. AJOG. 2012

Follow-up of Children Exposed In Utero to 17 α-Hydroxyprogesterone Caproate Compared With Placebo

*Allison T. Northen, RN, BSN, Gwendolyn S. Norman, RN, BSN, MPH, Kristine Anderson, RN, BSN, Lisa Moseley, RN, Michelle DiVito, RN, MSN, Margaret Cotroneo, RN, CCRC, Melissa Swain, RN, Sabine Bousleiman, RNC, MSN, Francee Johnson, RN, BSN, Karen Dorman, RN, MS, Cynthia Milluzzi, RN, BSN, Jo-Ann Tillinghast, RN, MSN, Marcia Kerr, RN, CCRC, Gail Mallett, BSN, CCRC, Elizabeth Thom, PhD, Susan Pagliaro, and Garland D. Anderson, MD, for the National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network**

OBJECTIVE: To assess whether there are evident adverse effects of 17 α-hydroxyprogesterone caproate after in utero exposure.

METHODS: This study evaluated surviving children of mothers who participated in a multicenter placebo-controlled trial of weekly intramuscular 17 α-hydroxyprogesterone caproate, with a 2:1 allocation to 17 α-hydroxyprogesterone caproate and placebo, respectively. The guardian was interviewed about the child's general health. Children underwent a physical examination and developmental screen with the Ages and Stages Questionnaire. Gender-specific roles were assessed with the Preschool Activities Inventory.

RESULTS: Of 348 eligible surviving children, 278 (80%) were available for evaluation (194 in the 17 α-hydroxyprogesterone caproate group and 84 in the placebo group). The mean age at follow-up was 48 months. No significant differences were seen in health status or physical examination, including genital anomalies, between 17 α-hydroxyprogesterone caproate and placebo children. Scores for gender-specific roles (Preschool Activities Inventory) were within the normal range and similar between 17 α-hydroxyprogesterone caproate and placebo groups.

CONCLUSION: 17 α-hydroxyprogesterone caproate seems to be safe for the fetus when administered in the second and third trimesters.

(Obstet Gynecol 2007;110:865–72)

LEVEL OF EVIDENCE: II

Results of the multicenter National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network study of 17 α-hydroxyprogesterone caproate for women with a prior spontaneous preterm birth demonstrated a significant reduction in the rate of recurrent spontaneous preterm birth at less than 37, 35, and 32 weeks gestation.[1] Renewed interest in 17 α-hydroxyprogesterone ca-

*For members of the NICHD MFMU Network, see the Appendix.

From the Departments of Obstetrics and Gynecology, Center for Women's Reproductive Health, University of Alabama at Birmingham, Birmingham, Alabama; Wayne State University, Detroit, Michigan; University of Utah, Salt Lake City, Utah; University of Texas Southwestern Medical Center, Dallas, Texas; Drexel University, Philadelphia, Pennsylvania; University of Pittsburgh, Pittsburgh, Pennsylvania; Wake Forest University, Winston-Salem, North Carolina; Columbia University, New York, New York; Ohio State University, Columbus, Ohio; University of North Carolina, Chapel Hill, North Carolina; Case Western Reserve University, Cleveland, Ohio; Brown University, Providence, Rhode Island; University of Texas at Houston, Houston, Texas; Northwestern University, Chicago, Illinois; the George Washington University Biostatistics Center, Washington, DC; National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland; and the University of Texas Medical Branch, Galveston, Texas.

Supported by grants from the National Institute of Child Health and Human Development (HD27869, HD27917, HD34208, HD34116, HD34136, HD21410, HD27860, HD40485, HD27915, HD40560, HD40544, HD40545, HD40512, HD36801).

The authors thank Mark Klebanoff, MD, for study design, protocol development, chart review and oversight; Paul Meis, MD, and Catherine Y. Spong, MD, for study design and protocol development; Valerija Momirova for protocol/data management and statistical analysis; and Dwight Rouse, MD, for manuscript preparation.

Corresponding author: Allison T. Northen, RN, BSN, Department of Obstetrics and Gynecology, University of Alabama at Birmingham, 1500 6th Avenue South CWRH 393, Birmingham, AL 35294-0024; e-mail: anorthen@uab.edu.

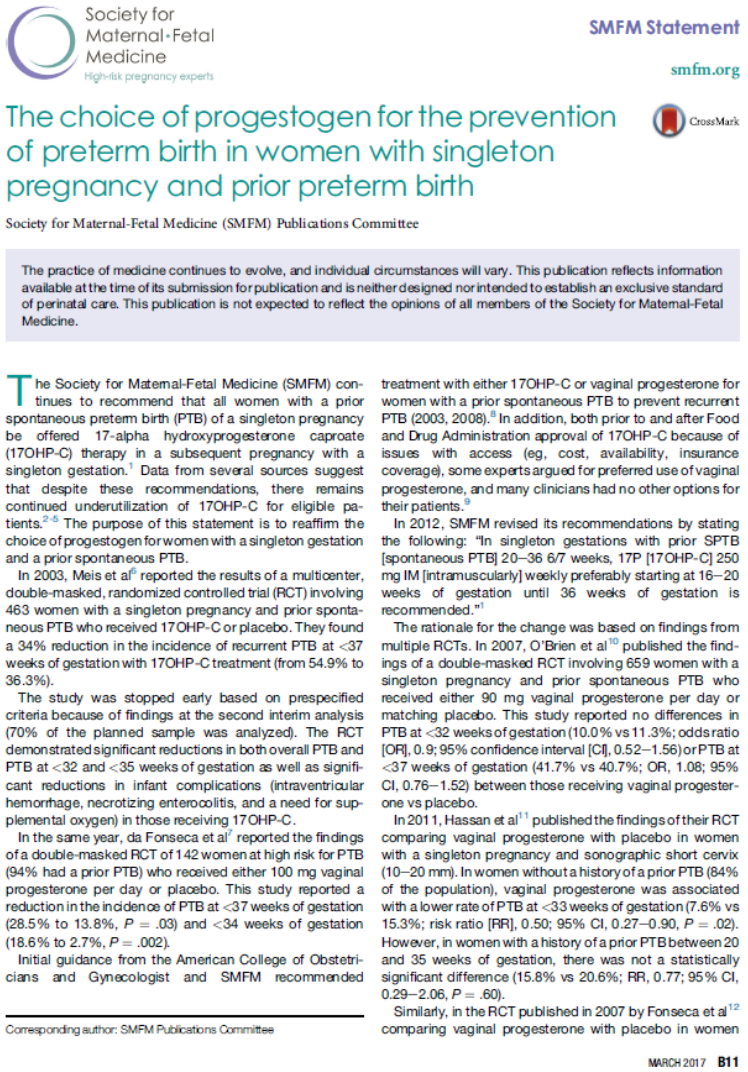
Financial Disclosure

The authors have no potential conflicts of interest to disclose.

ISSN: 0029-7844/07

Northen AT et al. Obstet Gynecol. 2007

In 2017…



Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Statement

smfm.org

The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

The practice of medicine continues to evolve, and individual circumstances will vary. This publication reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

The Society for Maternal-Fetal Medicine (SMFM) continues to recommend that all women with a prior spontaneous preterm birth (PTB) of a singleton pregnancy be offered 17-alpha hydroxyprogesterone caproate (17OHP-C) therapy in a subsequent pregnancy with a singleton gestation.[1] Data from several sources suggest that despite these recommendations, there remains continued underutilization of 17OHP-C for eligible patients.[2-5] The purpose of this statement is to reaffirm the choice of progestogen for women with a singleton gestation and a prior spontaneous PTB.

In 2003, Meis et al[6] reported the results of a multicenter, double-masked, randomized controlled trial (RCT) involving 463 women with a singleton pregnancy and prior spontaneous PTB who received 17OHP-C or placebo. They found a 34% reduction in the incidence of recurrent PTB at <37 weeks of gestation with 17OHP-C treatment (from 54.9% to 36.3%).

The study was stopped early based on prespecified criteria because of findings at the second interim analysis (70% of the planned sample was analyzed). The RCT demonstrated significant reductions in both overall PTB and PTB at <32 and <35 weeks of gestation as well as significant reductions in infant complications (intraventricular hemorrhage, necrotizing enterocolitis, and a need for supplemental oxygen) in those receiving 17OHP-C.

In the same year, da Fonseca et al[7] reported the findings of a double-masked RCT of 142 women at high risk for PTB (94% had a prior PTB) who received either 100 mg vaginal progesterone per day or placebo. This study reported a reduction in the incidence of PTB at <37 weeks of gestation (28.5% to 13.8%, $P = .03$) and <34 weeks of gestation (18.6% to 2.7%, $P = .002$).

Initial guidance from the American College of Obstetricians and Gynecologist and SMFM recommended treatment with either 17OHP-C or vaginal progesterone for women with a prior spontaneous PTB to prevent recurrent PTB (2003, 2008).[8] In addition, both prior to and after Food and Drug Administration approval of 17OHP-C because of issues with access (eg, cost, availability, insurance coverage), some experts argued for preferred use of vaginal progesterone, and many clinicians had no other options for their patients.[9]

In 2012, SMFM revised its recommendations by stating the following: "In singleton gestations with prior SPTB [spontaneous PTB] 20–36 6/7 weeks, 17P [17OHP-C] 250 mg IM [intramuscularly] weekly preferably starting at 16–20 weeks of gestation until 36 weeks of gestation is recommended."[1]

The rationale for the change was based on findings from multiple RCTs. In 2007, O'Brien et al[10] published the findings of a double-masked RCT involving 659 women with a singleton pregnancy and prior spontaneous PTB who received either 90 mg vaginal progesterone per day or matching placebo. This study reported no differences in PTB at <32 weeks of gestation (10.0% vs 11.3%; odds ratio [OR], 0.9; 95% confidence interval [CI], 0.52–1.56) or PTB at <37 weeks of gestation (41.7% vs 40.7%; OR, 1.08; 95% CI, 0.76–1.52) between those receiving vaginal progesterone vs placebo.

In 2011, Hassan et al[11] published the findings of their RCT comparing vaginal progesterone with placebo in women with a singleton pregnancy and sonographic short cervix (10–20 mm). In women without a history of a prior PTB (84% of the population), vaginal progesterone was associated with a lower rate of PTB at <33 weeks of gestation (7.6% vs 15.3%; risk ratio [RR], 0.50; 95% CI, 0.27–0.90, $P = .02$). However, in women with a history of a prior PTB between 20 and 35 weeks of gestation, there was not a statistically significant difference (15.8% vs 20.6%; RR, 0.77; 95% CI, 0.29–2.06, $P = .60$).

Similarly, in the RCT published in 2007 by Fonseca et al[12] comparing vaginal progesterone with placebo in women

Corresponding author: SMFM Publications Committee

SMFM Publications Committee. AJOG. 2017

At Parkland Health

Original Research ajog.org

OBSTETRICS

17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study

David B. Nelson, MD; Donald D. McIntire, PhD; Jeffrey McDonald, PhD; John Gard, PharmD; Paula Turrichi, BSBA, MS; Kenneth J. Leveno, MD

BACKGROUND: 17-alpha Hydroxyprogesterone caproate for prevention of recurrent preterm birth is recommended for use in the United States.

OBJECTIVE: We sought to assess the clinical effectiveness of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth ≤35 weeks compared to similar births in our obstetric population prior to the implementation of 17-alpha hydroxyprogesterone caproate.

STUDY DESIGN: This was a prospective cohort study of 17-alpha hydroxyprogesterone caproate in our obstetric population. The primary outcome was the recurrence of birth ≤35 weeks for the entire study cohort compared to a historical referent rate of 16.8% of recurrent preterm birth in our population. There were 3 secondary outcomes. First, did 17-alpha hydroxyprogesterone caproate modify a woman's history of preterm birth when taking into account her prior number and sequence of preterm and term births? Second, was recurrence of preterm birth related to 17-alpha hydroxyprogesterone caproate plasma concentration? Third, was duration of pregnancy modified by 17-alpha hydroxyprogesterone caproate treatment compared to a prior preterm birth?

RESULTS: From January 2012 through March 2016, 430 consecutive women with prior births ≤35 weeks were treated with 17-alpha hydroxyprogesterone caproate. Nearly two thirds of the women (N = 267) began injections ≤18 weeks and 394 (92%) received a scheduled weekly injection within 10 days of reaching 35 weeks or delivery. The overall rate of recurrent preterm birth was 25% (N = 106) for the entire cohort compared to the 16.8% expected rate ($P = 1.0$). The 3 secondary outcomes were also negative. First, 17-alpha hydroxyprogesterone caproate did not significantly reduce the rates of recurrence regardless of prior preterm birth number or sequence. Second, plasma concentrations of 17-alpha hydroxyprogesterone caproate were not different ($P = .17$ at 24 weeks; $P = .38$ at 32 weeks) between women delivered ≤35 weeks and those delivered later in pregnancy. Third, the mean (±SD) interval in weeks of recurrent preterm birth before 17-alpha hydroxyprogesterone caproate use was 0.4 ± 5.3 weeks and the interval of recurrent preterm birth after 17-alpha hydroxyprogesterone caproate treatment was 0.1 ± 4.7 weeks ($P = .63$). A side effect of weekly 17-alpha hydroxyprogesterone caproate injections was an increase in gestational diabetes. Specifically, the rate of gestational diabetes was 13.4% in 17-alpha hydroxyprogesterone caproate–treated women compared to 8% in case-matched controls ($P = .001$).

CONCLUSION: 17-alpha Hydroxyprogesterone caproate was ineffective for prevention of recurrent preterm birth and was associated with an increased rate of gestational diabetes.

Key words: efficacy, external validity, gestational diabetes, neonatal morbidity, prematurity, preterm birth, progesterone, progestogen, randomized trial

Introduction

Prevention of preterm birth is a major focus in obstetrics due to the burden of neonatal morbidity and mortality on mothers, infants, families, and society both medically and financially. Dollar costs due to prematurity in the United States in 2006 were estimated to be >$26 billion.[1] Moreover, the consequences of prematurity include long-term neurological complications due to immaturity related injuries to the brain.[2] Consequently, development of interventions to reduce the rate of preterm birth have been emphasized in the United States for several decades. A recent example is the widespread use of progestogens to prevent preterm birth.[3-9]

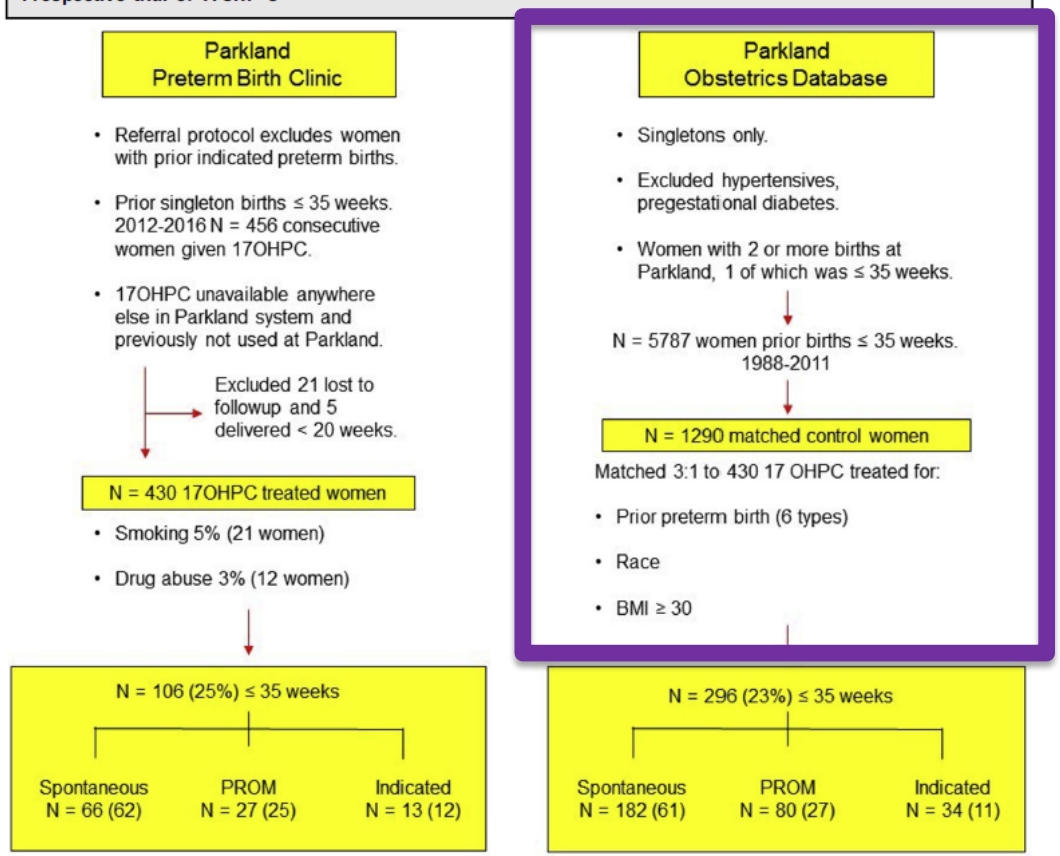
17-alpha Hydroxyprogesterone caproate (17OHP-C), a synthetic progestogen, is the first and only agent to date approved for marketing by the US Food and Drug Administration (FDA) for prevention of recurrent preterm birth.[10] This approval stems from a trial by Meis and colleagues[3] published in 2003. Following FDA approval, the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) endorsed use of 17OHP-C for prevention of recurrent preterm birth in singleton gestations.[11,12] Most recently (January 2017), the SMFM Publications Committee recommended 17OHP-C be used for prevention of recurrent preterm birth and that vaginal progesterone should not be considered a substitute for 17OHP-C.[13] The SMFM Publications Committee also concluded that despite their recommendations, there continued to be underutilization of 17OHP-C.[13] It is important to emphasize that the FDA approval of 17OHP-C was under a regulatory pathway (Subpart H of the FDA Code of Regulations) used when the decision is made on the basis of a surrogate endpoint—delivery <37 weeks of gestation in this case—and was deemed to require further studies.[14] In fact, another placebo-controlled randomized trial of 17OHP-C is in progress in the United States and elsewhere with the FDA-preferred primary endpoint of delivery <35 weeks' gestation. Details of this ongoing trial titled, "Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous

Cite this article as: Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.02.025

FIGURE
Prospective trial of 17OHP-C



Methods and results of before/after prospective observational trial of efficacy of 17-alpha hydroxyprogesterone caproate (OHPC) performed at Parkland Hospital.

BMI, body mass index; *PROM*, premature rupture of membranes.

Nelson DB, McIntire DD, Leveno KJ. Reply. Am J Obstet Gynecol 2018;219:218-220.

Nelson et al. AJOG. June 2017

UTSouthwestern Medical Center

Recognizing the importance of history

CAOG PAPERS www.AJOG.org

Recurrence risk for preterm delivery

Julie McManemy, MD; Erinn Cooke, MPH; Erol Amon, MD; Terry Leet, PhD

OBJECTIVE: To estimate recurrence risk of preterm delivery in third births.

STUDY DESIGN: We conducted a population-based cohort study of Missouri mothers who delivered 3 consecutive singleton live births during 1989-1997. The recurrence risk was computed for 4 cohorts based on prior preterm delivery status and adjusted using Mantel-Haenszel stratified analysis.

RESULTS: The study population included 19,025 third births. The recurrence risk ranged from 42% (for women with 2 prior preterm deliveries), through 21% (term/preterm) and 13% (preterm/term), to 5% (term/term). The recurrence risk was highest (57%) for women with 2 prior very preterm deliveries (21-31 weeks) and lowest (33%) for those with 2 prior moderate preterm deliveries (32-36 weeks). The recurrence risk was less pronounced for women with 1 prior very or moderate preterm delivery.

CONCLUSION: These data show a strong association between prior preterm delivery and recurrence risk, which is affected by the frequency, order, and severity of prior preterm births.

Key words: gestational age at delivery, prematurity, preterm delivery, recurrence, risk factors

Cite this article as: McManemy J, Cooke E, Amon E, Leet T. Recurrence risk for preterm delivery. Am J Obstet Gynecol 2007;196:576.e1-576.e7.

Preterm delivery is the leading cause of morbidity and mortality in newborns.[1,2] Premature infants are prone to developmental and cognitive abnormalities. Infants who deliver at earlier gestations incur longer length of stays in the hospital and higher health care costs. Furthermore, the incidence of preterm delivery has significantly increased. In the United States, the risk for preterm birth (<37 weeks of gestation) steadily increased from 1992 to 2002.[3] In 2003, 12.1% of live births in the United States are born preterm. This concerning trend is a major public health issue and has led to the recommendation in Healthy People 2010 to decrease the risk of preterm delivery to less than 7.6% of live births.[4]

Previous studies have shown that prior preterm delivery confers an increased risk of recurrent preterm delivery in subsequent pregnancies.[4-21] Evidence from population-based studies regarding the risk of recurrent preterm delivery in multiparous women is largely limited to first and second pregnancies, with insufficient data relating to gestational age.[6,13,22] Little is known about the risk of a third preterm delivery. Bakketeig et al[23] found that the risk of preterm delivery in the third birth was similar to the risks for a second preterm delivery. They also demonstrated that the risk of a third preterm baby was high (28%) when the first and second births were preterm; however, that study did not determine if the risk of a third preterm baby was modified by gestational age of prior preterm deliveries. Other studies delineating the risk of recurrent preterm labor in third and subsequent pregnancies were limited to hospital-based studies, which may not be generalizable to the general population.[9,10,12,24]

Our objective was to evaluate the risk of preterm delivery in third birth and to determine if the risk is was modified by frequency, severity, and order of prior preterm deliveries. We hypothesized that a history of previous preterm delivery would confer an increased risk of preterm delivery in third birth and that the risk of preterm delivery would increase with decreasing gestational age of prior births.

Materials and Methods

We conducted a population-based cohort study of preterm births in multiparous women. The study population was obtained from the Missouri maternally linked cohort, which links sibling birth certificate data to common maternal identifiers.[25] The study population included all mothers who were residents of Missouri and who delivered 3 consecutive singleton live births (>20 weeks gestation) during 1989-1997. The study was restricted to this 9-year period because the clinical estimate of gestational age at delivery was first recorded on the Missouri birth certificate in 1989 and the last year of available data for this cohort was 1997. Mothers with multiple gestations were excluded from the study, to eliminate nonindependent events. Mothers with missing information regarding gestational age at delivery or other potential risk factors (listed below) were excluded from our sample.

From the Department of Pediatrics, Division of Emergency Medicine, Washington University School of Medicine (Dr McManemy); the Department of Community Health, School of Public Health, Saint Louis University (Drs McManemy and Leet and Ms Cooke); and the Department of Obstetrics, Gynecology, and Women's Health, Saint Louis University School of Medicine (Drs Amon and Leet), St Louis, MO.

Presented at the 73rd Annual Meeting of the Central Association of Obstetricians and Gynecologists, Las Vegas, NV, Oct. 18-21, 2006.

Received July 7, 2006; accepted Jan. 28, 2007.

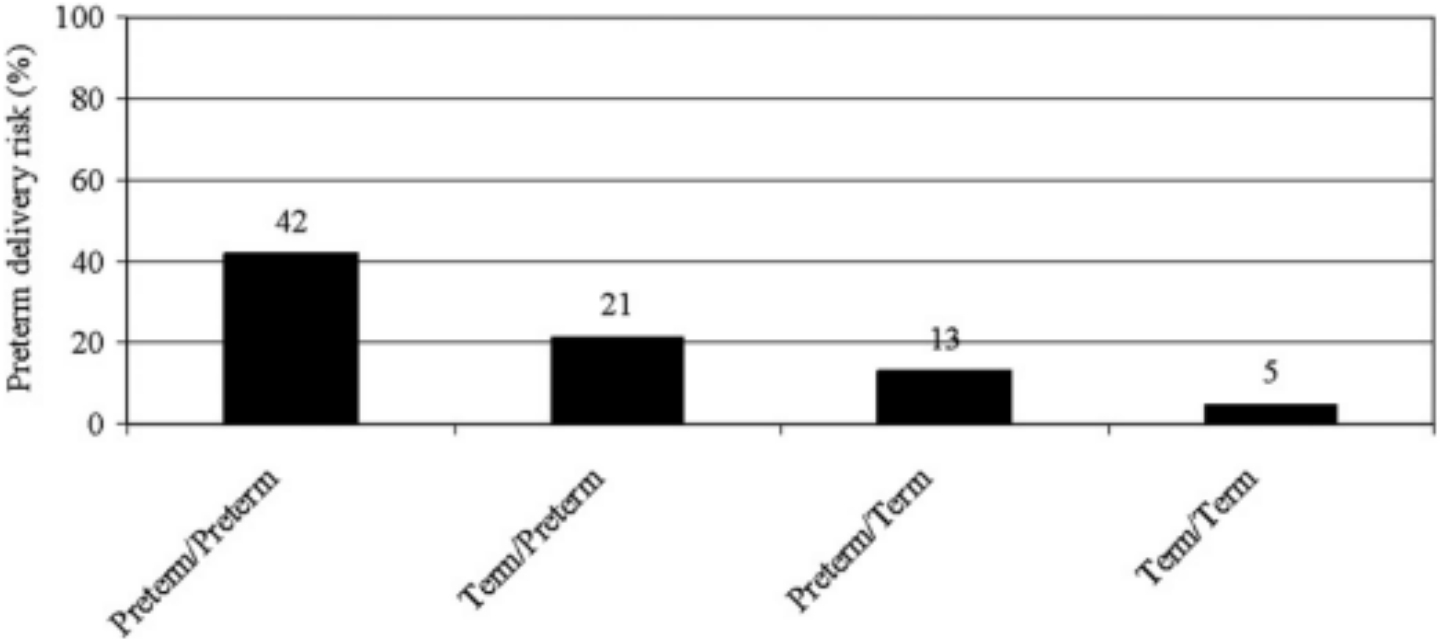
Reprints not available from the authors.

0002-9378/$32.00

doi: 10.1016/j.ajog.2007.01.039

FIGURE 1

Preterm delivery risk for third births in cohorts 1-4



McManemy J et al. AJOG. 2007

UT Southwestern Medical Center

Recognizing the importance of history

Recurrence of Preterm Birth in Singleton and Twin Pregnancies

Steven L. Bloom, MD, Nicole P. Yost, MD, Donald D. McIntire, PhD, and Kenneth J. Leveno, MD

OBJECTIVE: To assess recurrence of preterm birth and its impact on an obstetric population.

METHODS: Women with consecutive births at our hospital beginning with their first pregnancy were identified (n = 15,945). The first pregnancy was categorized as delivered between 24 and 34 weeks' gestation or 35 weeks or beyond, singleton or twin, and spontaneous or induced. The risk of preterm delivery in these same women during subsequent pregnancies was then analyzed.

RESULTS: Compared with women who delivered a singleton at or beyond 35 weeks' gestation in their first pregnancy, those who delivered a singleton before 35 weeks were at a significant increased risk for recurrence (odds ratio [OR] 5.6, 95% confidence interval [CI] 4.5, 7.0), whereas those who delivered twins were not (OR 1.9, 95% CI 0.46, 8.14). The OR for recurrent spontaneous preterm birth presenting with intact membranes was 7.9 (95% CI 5.6, 11.3) compared with 5.5 (95% CI 3.2, 9.4) with ruptured membranes. Of those women with a recurrent preterm birth, 49% delivered within 1 week of the gestational age of their first delivery and 70% delivered within 2 weeks. Among 15,863 nulliparous women with singleton births at their first delivery, a history of preterm birth in that pregnancy could predict only 10% of the preterm births that ultimately occurred in the entire obstetric population.

CONCLUSION: In a population-based study at our hospital, women who initially delivered preterm and thus were identified to be at risk for recurrence ultimately accounted for only 10% of the prematurity problem in the cohort. (Obstet Gynecol 2001;98:379–85. © 2001 by the American College of Obstetricians and Gynecologists.)

A history of a prior preterm birth is generally accepted to be a significant risk factor for recurrence in a future pregnancy. With the recent advent of tests designed to improve the identification of women at risk for preterm delivery, the risk associated with history alone may become inappropriately minimized. In a recent multicenter investigation, for example, the odds ratios (OR) for preterm birth less than 35 weeks' gestation associated with markers of preterm delivery such as detection of fetal fibronectin in cervical secretions (OR 5.2), ultrasonic shortening of the cervix (OR 4.1), and colonization of the genital tract with bacterial vaginosis (OR 1.3) were all lower than the risk of recurrence based solely upon a history of prior preterm birth (OR 5.8).[1]

Although a general, nonspecific history of preterm birth is accepted to be a risk factor for recurrence, there is little information on the recurrence risk for specific types of prior preterm deliveries.[2] Moreover, given the recent increase in twin gestations,[3] it is unclear if spontaneous preterm delivery of twins modifies a woman's risk for a subsequent preterm birth. Stated differently, does a history of a spontaneous preterm twin delivery convey the same risk for recurrence as does a history of a spontaneous preterm singleton delivery? Lastly, what is the contribution of women with recurrent preterm delivery to the overall problem of prematurity in an obstetric population?

Since 1988, we have collected information on pregnancy outcomes for all women delivering at our institution. With over 10 years of computerized data involving nearly 170,000 women, many of whom with more than one delivery at our hospital, we had the opportunity to analyze the reproductive histories of a cohort of over 15,000 women beginning with their first delivery and including all subsequent consecutive pregnancies. The purpose of this analysis was to measure the risk of recurrent preterm birth based on 1) whether the first delivery was a preterm singleton or twin, 2) the labor was spontaneous or induced, 3) the timing of recurrence, and 4) the overall contribution these women made to preterm births in the study cohort.

MATERIALS AND METHODS

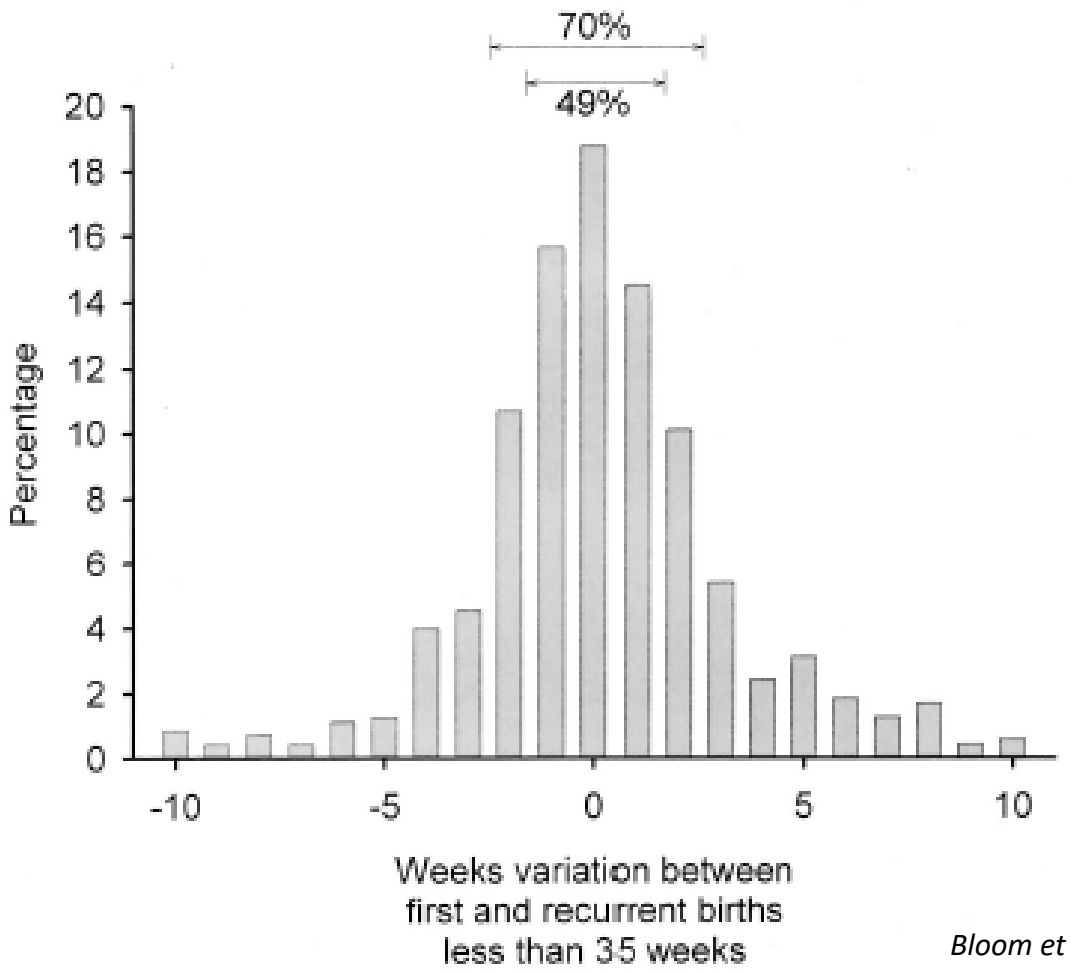
Women with consecutive pregnancies, beginning with their first birth, and who were delivered at our hospital between January 1, 1988, and December 31, 1999, were identified using a computerized database. This database

From the Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, Texas.

VOL. 98, NO. 3, SEPTEMBER 2001

0029-7844/01/$20.00 PII S0029-7844(01)01466-1

1st birth < 35 weeks→ **16%** risk next birth < 35 weeks



Bloom et al. Obstet Gynecol. 2001

UTSouthwestern Medical Center

At Parkland Health

Original Research ajog.org

OBSTETRICS

17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study

David B. Nelson, MD; Donald D. McIntire, PhD; Jeffrey McDonald, PhD; John Gard, PharmD; Paula Turrichi, BSBA, MS; Kenneth J. Leveno, MD

BACKGROUND: 17-alpha Hydroxyprogesterone caproate for prevention of recurrent preterm birth is recommended for use in the United States.

OBJECTIVE: We sought to assess the clinical effectiveness of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth ≤35 weeks compared to similar births in our obstetric population prior to the implementation of 17-alpha hydroxyprogesterone caproate.

STUDY DESIGN: This was a prospective cohort study of 17-alpha hydroxyprogesterone caproate in our obstetric population. The primary outcome was the recurrence of birth ≤35 weeks for the entire study cohort compared to a historical referent rate of 16.8% of recurrent preterm birth in our population. There were 3 secondary outcomes. First, did 17-alpha hydroxyprogesterone caproate modify a woman's history of preterm birth when taking into account her prior number and sequence of preterm and term births? Second, was recurrence of preterm birth related to 17-alpha hydroxyprogesterone caproate plasma concentration? Third, was duration of pregnancy modified by 17-alpha hydroxyprogesterone caproate treatment compared to a prior preterm birth?

RESULTS: From January 2012 through March 2016, 430 consecutive women with prior births ≤35 weeks were treated with 17-alpha hydroxyprogesterone caproate. Nearly two thirds of the women (N = 267) began injections ≤18 weeks and 394 (92%) received a scheduled weekly injection within 10 days of reaching 35 weeks or delivery. The overall rate of recurrent preterm birth was 25% (N = 106) for the entire cohort compared to the 16.8% expected rate ($P = 1.0$). The 3 secondary outcomes were also negative. First, 17-alpha hydroxyprogesterone caproate did not significantly reduce the rates of recurrence regardless of prior preterm birth number or sequence. Second, plasma concentrations of 17-alpha hydroxyprogesterone caproate were not different ($P = .17$ at 24 weeks; $P = .38$ at 32 weeks) between women delivered ≤35 weeks and those delivered later in pregnancy. Third, the mean (±SD) interval in weeks of recurrent preterm birth before 17-alpha hydroxyprogesterone caproate use was 0.4 ± 5.3 weeks and the interval of recurrent preterm birth after 17-alpha hydroxyprogesterone caproate treatment was 0.1 ± 4.7 weeks ($P = .63$). A side effect of weekly 17-alpha hydroxyprogesterone caproate injections was an increase in gestational diabetes. Specifically, the rate of gestational diabetes was 13.4% in 17-alpha hydroxyprogesterone caproate–treated women compared to 8% in case-matched controls ($P = .001$).

CONCLUSION: 17-alpha Hydroxyprogesterone caproate was ineffective for prevention of recurrent preterm birth and was associated with an increased rate of gestational diabetes.

Key words: efficacy, external validity, gestational diabetes, neonatal morbidity, prematurity, preterm birth, progesterone, progestogen, randomized trial

Introduction

Prevention of preterm birth is a major focus in obstetrics due to the burden of neonatal morbidity and mortality on mothers, infants, families, and society both medically and financially. Dollar costs due to prematurity in the United States in 2006 were estimated to be > $26 billion.[1] Moreover, the consequences of prematurity include long-term neurological complications due to immaturity related injuries to the brain.[2] Consequently, development of interventions to reduce the rate of preterm birth have been emphasized in the United States for several decades. A recent example is the widespread use of progestogens to prevent preterm birth.[3-9]

17-alpha Hydroxyprogesterone caproate (17OHP-C), a synthetic progestogen, is the first and only agent to date approved for marketing by the US Food and Drug Administration (FDA) for prevention of recurrent preterm birth.[10] This approval stems from a trial by Meis and colleagues[3] published in 2003. Following FDA approval, the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) endorsed use of 17OHP-C for prevention of recurrent preterm birth in singleton gestations.[11,12] Most recently (January 2017), the SMFM Publications Committee recommended 17OHP-C be used for prevention of recurrent preterm birth and that vaginal progesterone should not be considered a substitute for 17OHP-C.[13] The SMFM Publications Committee also concluded that despite their recommendations, there continued to be underutilization of 17OHP-C.[13] It is important to emphasize that the FDA approval of 17OHP-C was under a regulatory pathway (Subpart H of the FDA Code of Regulations) used when the decision is made on the basis of a surrogate endpoint—delivery <37 weeks of gestation in this case—and was deemed to require further studies.[14] In fact, another placebo-controlled randomized trial of 17OHP-C is in progress in the United States and elsewhere with the FDA-preferred primary endpoint of delivery <35 weeks' gestation. Details of this ongoing trial titled, "Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous

Cite this article as: Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.02.025

TABLE 2
Obstetric history of 430 women with births ≤35 weeks and recurrence rates after 17-alpha hydroxyprogesterone caproate treatment compared to historical cohort of 5787 women with prior preterm birth at Parkland Hospital

	No 17OHP-C	17OHP-C treated			
			Recurrence		
Prior birth <35 wk	Historical cohort recurrence rate[a]	No. of women	No. of women	Rate	*P* value[b]
Overall	16.8%	430	106	25%	1.0
Para 1	18%	141	44	31%	1.0
Para 2					
Both ≤35 wk	43%	48	20	42%	.49
Only second birth ≤35 wk	17%	52	11	21%	.84
Only first birth ≤35 wk	11%	39	2	5%	.18
Para ≥3					
All ≤35 wk	45%	27	12	44%	.56
Other sequences of ≤35 wk	12%	123	17	14%	.78

17OHP-C, 17-alpha hydroxyprogesterone cap

[a] Derived from Parkland obstetric population for 1988 through 2011 prior to introduction of 17OHP-C; [b] *P* values are 1-sided.

Nelson et al. Lack of effectiveness of 17OHP-C in prevention of recurrent preterm birth. Am J Obstet Gynecol 2017.

Nelson et al. AJOG. June 2017

UTSouthwestern Medical Center

At Parkland Health

Original Research ajog.org

OBSTETRICS

17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study

David B. Nelson, MD; Donald D. McIntire, PhD; Jeffrey McDonald, PhD; John Gard, PharmD; Paula Turrichi, BSBA, MS; Kenneth J. Leveno, MD

BACKGROUND: 17-alpha Hydroxyprogesterone caproate for prevention of recurrent preterm birth is recommended for use in the United States.

OBJECTIVE: We sought to assess the clinical effectiveness of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth ≤35 weeks compared to similar births in our obstetric population prior to the implementation of 17-alpha hydroxyprogesterone caproate.

STUDY DESIGN: This was a prospective cohort study of 17-alpha hydroxyprogesterone caproate in our obstetric population. The primary outcome was the recurrence of birth ≤35 weeks for the entire study cohort compared to a historical referent rate of 16.8% of recurrent preterm birth in our population. There were 3 secondary outcomes. First, did 17-alpha hydroxyprogesterone caproate modify a woman's history of preterm birth when taking into account her prior number and sequence of preterm and term births? Second, was recurrence of preterm birth related to 17-alpha hydroxyprogesterone caproate plasma concentration? Third, was duration of pregnancy modified by 17-alpha hydroxyprogesterone caproate treatment compared to a prior preterm birth?

RESULTS: From January 2012 through March 2016, 430 consecutive women with prior births ≤35 weeks were treated with 17-alpha hydroxyprogesterone caproate. Nearly two thirds of the women (N = 267) began injections ≤18 weeks and 394 (92%) received a scheduled weekly injection within 10 days of reaching 35 weeks or delivery. The overall rate of recurrent preterm birth was 25% (N = 106) for the entire cohort compared to the 16.8% expected rate ($P = 1.0$). The 3 secondary outcomes were also negative. First, 17-alpha hydroxyprogesterone caproate did not significantly reduce the rates of recurrence regardless of prior preterm birth number or sequence. Second, plasma concentrations of 17-alpha hydroxyprogesterone caproate were not different ($P = .17$ at 24 weeks; $P = .38$ at 32 weeks) between women delivered ≤35 weeks and those delivered later in pregnancy. Third, the mean (±SD) interval in weeks of recurrent preterm birth before 17-alpha hydroxyprogesterone caproate use was 0.4 ± 5.3 weeks and the interval of recurrent preterm birth after 17-alpha hydroxyprogesterone caproate treatment was 0.1 ± 4.7 weeks ($P = .63$). A side effect of weekly 17-alpha hydroxyprogesterone caproate injections was an increase in gestational diabetes. Specifically, the rate of gestational diabetes was 13.4% in 17-alpha hydroxyprogesterone caproate–treated women compared to 8% in case-matched controls ($P = .001$).

CONCLUSION: 17-alpha Hydroxyprogesterone caproate was ineffective for prevention of recurrent preterm birth and was associated with an increased rate of gestational diabetes.

Key words: efficacy, external validity, gestational diabetes, neonatal morbidity, prematurity, preterm birth, progesterone, progestogen, randomized trial

Introduction

Prevention of preterm birth is a major focus in obstetrics due to the burden of neonatal morbidity and mortality on mothers, infants, families, and society both medically and financially. Dollar costs due to prematurity in the United States in 2006 were estimated to be > $26 billion.[1] Moreover, the consequences of prematurity include long-term neurological complications due to immaturity related injuries to the brain.[2] Consequently, development of interventions to reduce the rate of preterm birth have been emphasized in the United States for several decades. A recent example is the widespread use of progestogens to prevent preterm birth.[3-9]

17-alpha Hydroxyprogesterone caproate (17OHP-C), a synthetic progestogen, is the first and only agent to date approved for marketing by the US Food and Drug Administration (FDA) for prevention of recurrent preterm birth.[10] This approval stems from a trial by Meis and colleagues[3] published in 2003. Following FDA approval, the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) endorsed use of 17OHP-C for prevention of recurrent preterm birth in singleton gestations.[11,12] Most recently (January 2017), the SMFM Publications Committee recommended 17OHP-C be used for prevention of recurrent preterm birth and that vaginal progesterone should not be considered a substitute for 17OHP-C.[13] The SMFM Publications Committee also concluded that despite their recommendations, there continued to be underutilization of 17OHP-C.[13] It is important to emphasize that the FDA approval of 17OHP-C was under a regulatory pathway (Subpart H of the FDA Code of Regulations) used when the decision is made on the basis of a surrogate endpoint—delivery <37 weeks of gestation in this case—and was deemed to require further studies.[14] In fact, another placebo-controlled randomized trial of 17OHP-C is in progress in the United States and elsewhere with the FDA-preferred primary endpoint of delivery <35 weeks' gestation. Details of this ongoing trial titled, "Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous

Cite this article as: Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2017.02.025

TABLE 2

Obstetric history of 430 women with births ≤35 weeks and recurrence rates after 17-alpha hydroxyprogesterone caproate treatment compared to historical cohort of 5787 women with prior preterm birth at Parkland Hospital

	No 17OHP-C	17OHP-C treated			
			Recurrence		
Prior birth <35 wk	Historical cohort recurrence rate[a]	No. of women	No. of women	Rate	*P* value[b]
Overall	16.8%	430	106	25%	1.0
Para 1	18%	141	44	31%	1.0
Para 2					
Both ≤35 wk	43%	48	20	42%	.49
Only second birth ≤35 wk	17%	52	11	21%	.84
Only first birth ≤35 wk	11%	39	2	5%	.18
Para ≥3					
All ≤35 wk	45%	27	12	44%	.56
Other sequences of ≤35 wk	12%	123	17	14%	.78

17OHP-C, 17-alpha hydroxyprogesterone caproate.

[a] Derived from Parkland obstetric population for 1988 through 2011 prior to introduction of 17OHP-C; [b] *P* values are 1-sided.

Nelson et al. Lack of effectiveness of 17OHP-C in prevention of recurrent preterm birth. Am J Obstet Gynecol 2017.

Nelson et al. AJOG. June 2017

UTSouthwestern Medical Center

At Parkland Health

Original Research ajog.org

OBSTETRICS

17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study

David B. Nelson, MD; Donald D. McIntire, PhD; Jeffrey McDonald, PhD; John Gard, PharmD; Paula Turrichi, BSBA, MS; Kenneth J. Leveno, MD

BACKGROUND: 17-alpha Hydroxyprogesterone caproate for prevention of recurrent preterm birth is recommended for use in the United States.

OBJECTIVE: We sought to assess the clinical effectiveness of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth ≤35 weeks compared to similar births in our obstetric population prior to the implementation of 17-alpha hydroxyprogesterone caproate.

STUDY DESIGN: This was a prospective cohort study of 17-alpha hydroxyprogesterone caproate in our obstetric population. The primary outcome was the recurrence of birth ≤35 weeks for the entire study cohort compared to a historical referent rate of 16.8% of recurrent preterm birth in our population. There were 3 secondary outcomes. First, did 17-alpha hydroxyprogesterone caproate modify a woman's history of preterm birth when taking into account her prior number and sequence of preterm and term births? Second, was recurrence of preterm birth related to 17-alpha hydroxyprogesterone caproate plasma concentration? Third, was duration of pregnancy modified by 17-alpha hydroxyprogesterone caproate treatment compared to a prior preterm birth?

RESULTS: From January 2012 through March 2016, 430 consecutive women with prior births ≤35 weeks were treated with 17-alpha hydroxyprogesterone caproate. Nearly two thirds of the women (N = 267) began injections ≤18 weeks and 394 (92%) received a scheduled weekly injection within 10 days of reaching 35 weeks or delivery. The overall rate of recurrent preterm birth was 25% (N = 106) for the entire cohort compared to the 16.8% expected rate ($P = 1.0$). The 3 secondary outcomes were also negative. First, 17-alpha hydroxyprogesterone caproate did not significantly reduce the rates of recurrence regardless of prior preterm birth number or sequence. Second, plasma concentrations of 17-alpha hydroxyprogesterone caproate were not different ($P = .17$ at 24 weeks; $P = .38$ at 32 weeks) between women delivered ≤35 weeks and those delivered later in pregnancy. Third, the mean (±SD) interval in weeks of recurrent preterm birth before 17-alpha hydroxyprogesterone caproate use was 0.4 ± 5.3 weeks and the interval of recurrent preterm birth after 17-alpha hydroxyprogesterone caproate treatment was 0.1 ± 4.7 weeks ($P = .63$). A side effect of weekly 17-alpha hydroxyprogesterone caproate injections was an increase in gestational diabetes. Specifically, the rate of gestational diabetes was 13.4% in 17-alpha hydroxyprogesterone caproate–treated women compared to 8% in case-matched controls ($P = .001$).

CONCLUSION: 17-alpha Hydroxyprogesterone caproate was ineffective for prevention of recurrent preterm birth and was associated with an increased rate of gestational diabetes.

Key words: efficacy, external validity, gestational diabetes, neonatal morbidity, prematurity, preterm birth, progesterone, progestogen, randomized trial

Introduction

Prevention of preterm birth is a major focus in obstetrics due to the burden of neonatal morbidity and mortality on mothers, infants, families, and society both medically and financially. Dollar costs due to prematurity in the United States in 2006 were estimated to be > $26 billion.[1] Moreover, the consequences of prematurity include long-term neurological complications due to immaturity related injuries to the brain.[2] Consequently, development of interventions to reduce the rate of preterm birth have been emphasized in the United States for several decades. A recent example is the widespread use of progestogens to prevent preterm birth.[3-9]

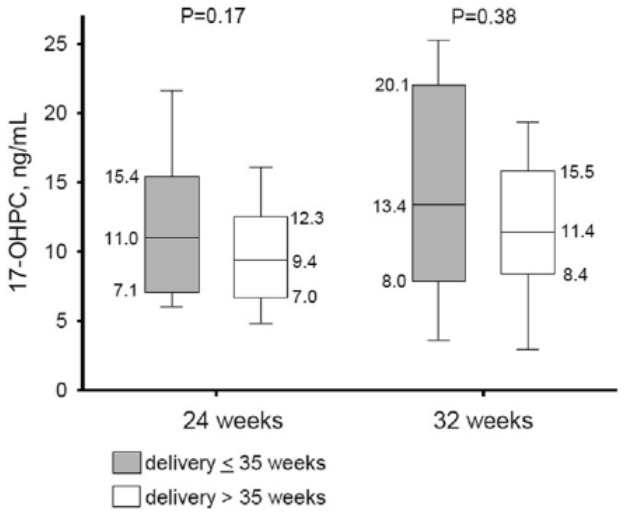
17-alpha Hydroxyprogesterone caproate (17OHP-C), a synthetic progestogen, is the first and only agent to date approved for marketing by the US Food and Drug Administration (FDA) for prevention of recurrent preterm birth.[10] This approval stems from a trial by Meis and colleagues[3] published in 2003. Following FDA approval, the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) endorsed use of 17OHP-C for prevention of recurrent preterm birth in singleton gestations.[11,12] Most recently (January 2017), the SMFM Publications Committee recommended 17OHP-C be used for prevention of recurrent preterm birth and that vaginal progesterone should not be considered a substitute for 17OHP-C.[13] The SMFM Publications Committee also concluded that despite their recommendations, there continued to be underutilization of 17OHP-C.[13] It is important to emphasize that the FDA approval of 17OHP-C was under a regulatory pathway (Subpart H of the FDA Code of Regulations) used when the decision is made on the basis of a surrogate endpoint—delivery <37 weeks of gestation in this case—and was deemed to require further studies.[14] In fact, another placebo-controlled randomized trial of 17OHP-C is in progress in the United States and elsewhere with the FDA-preferred primary endpoint of delivery <35 weeks' gestation. Details of this ongoing trial titled, "Confirmatory Study of 17P Versus Vehicle for the Prevention of Preterm Birth in Women with a Previous Singleton Spontaneous

Cite this article as: Nelson DB, McIntire DD, McDonald J, et al. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol 2017;volume:x.ex-x.ex.

0002-9378/$36.00

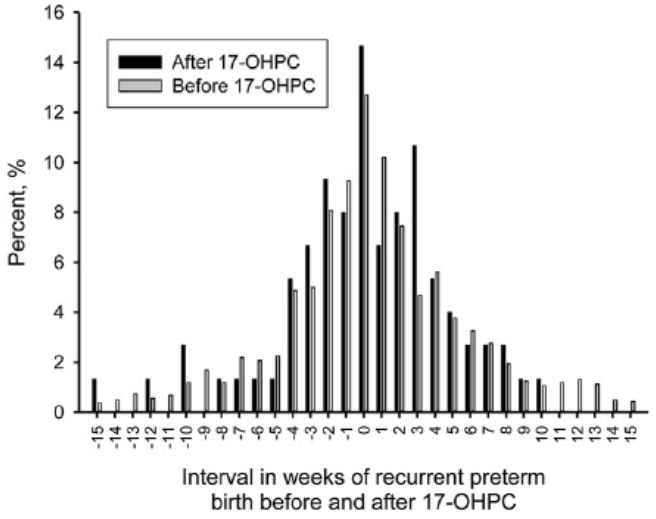
http://dx.doi.org/10.1016/j.ajog.2017.02.025

FIGURE 2
17 OHP-C plasma concentration measured at 24 and 32 weeks



Recurrent preterm births according to 17-alpha hydroxyprogesterone caproate (17 OHP-C) plasma drug concentrations measured at 24 and 32 weeks' gestation. Data are shown as median for treated women delivered ≤35 weeks (shaded) and >35 weeks (not shaded) on therapy.

FIGURE 3
Duration of pregnancy in women delivered ≤ 35 weeks with 17 OHP-C treatment



Duration of pregnancy in women delivered ≤35 weeks on 17-alpha hydroxyprogesterone caproate (17 OHP-C) compared to similar women with recurrent preterm births from 1988 through 2011 but untreated with 17 OHP-C.

Nelson et al. AJOG. June 2017

UTSouthwestern Medical Center

703 **Recurrent spontaneous preterm birth risk is not associated with 17-alpha hydroxyprogesterone caproate levels**

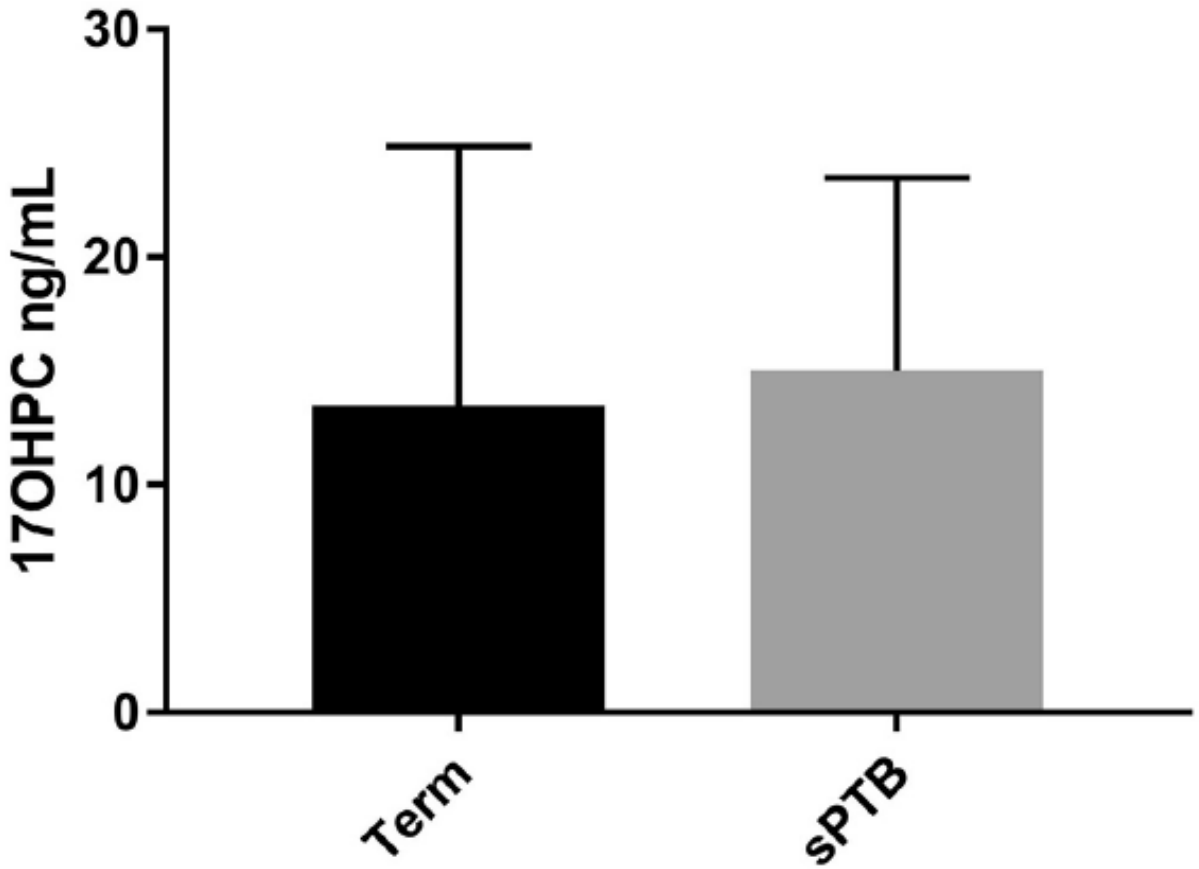
Katheryne L. Downes[1], Raman Venkataramanan[2], Steve Caritis[2], Michal A. Elovitz[1]
[1]University of Pennsylvania, Philadelphia, PA, [2]University of Pittsburg, Pittsburg, PA

OBJECTIVE: A 2003 randomized clinical trial demonstrated efficacy of 17-alpha hydroxyprogesterone caproate (17OHPC) in reducing recurrent spontaneous preterm birth (sPTB) (Meis et al NEJM). However, a recent large observational study failed to demonstrate a benefit from 17OHPC use (Nelson et al, AJOG 2017) and no difference in 17OHPC levels. Some studies suggest that inadequate 17POHPC exposure may be the cause of reduced efficacy of the drug. In a large cohort, we sought to assess if 17OHPC levels were associated with recurrent sPTB.

STUDY DESIGN: A prospective cohort of high risk women (The PRoMISE study) enrolled women with a documented prior sPTB (16-36 weeks). Biospecimens were collected at 2 time points: 16-20 weeks (prior to starting 17P) and 8 weeks later. Maternal blood was drawn at the 2nd visit for 17OHPC and progesterone levels. 17-OHPC and progesterone were measured using validated HPLC-MS-MS method. (The standard curve was linear over a concentration range of 1-200ng/ml. The CV of this assay is <10%. Fisher exact and Wilcoxon-rank sum tests were used to complete univariate comparisons. 17OHPC level was log transformed for regression analysis. Relative risk of sPTB was estimated using modified Poisson regression adjusting for number of prior 2nd trimester losses and sPTB, cerclage, race, earliest GA at prior preterm birth and obesity.

RESULTS: Out of 255 women, the overall rate of sPTB was 22.3% and was not significantly different between women who did and did not receive 17OHPC (24.9% vs. 17.1%, p=0.20). Among 140 women receiving 17P, the median and interquartile range of plasma levels was 11.5 (7.7-16.5), and in univariate analysis was not significantly different in those having a term or sPTB delivery (median 11 vs. 12, p=0.20). Progesterone levels were also similar between the groups. 17OHPC levels were also not different by GA at earliest prior PTB After adjusting for covariates, increasing levels of 17OHPC were associated with higher risk of sPTB (RR=1.55, 95% CI: 1.02-2.34, p=0.04).

CONCLUSION: These findings suggest that higher 17OPHC levels are not associated with lower rates of recurrent SPTB and that higher levels may actually increase the risk. Future clinical trials should be performed to determine if 17OPHC is an effective therapeutic strategy to reduce recurrent sPTB. (Penn Precision Medicine Grant)



Downes KL, Raman V, Caritis S, et al. Recurrent spontaneous preterm birth risk is not associated with 17-alpha hydroxyprogesterone caproate. Am J Obstet Gynecol 2018;218:S422–3.

PROLONG Trial

PROLONG

Published online: 25.10.2019

THIEME OPEN ACCESS

Original Article

17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial

Sean C. Blackwell, MD[1] Cynthia Gyamfi-Bannerman, MD, MS[2] Joseph R. Biggio Jr., MD[3] Suneet P. Chauhan, MD[1] Brenna L. Hughes, MD[4] Judette M. Louis, MD[5] Tracy A. Manuck, MD[6] Hugh S. Miller, MD[7] Anita F. Das, PhD[8] George R. Saade, MD[9] Peter Nielsen, MD[10] Jeff Baker, MD[11] Oleksandr M. Yuzko, MD, PhD[12] Galyna I. Reznichenko, MD, PhD[13] Nataliya Y. Reznichenko, MD, PhD[13] Oleg Pekarev, MD, PhD[14] Nina Tatarova, MD, PhD[15] Jennifer Gudeman, PharmD[16] Robert Birch, PhD[17] Michael J. Jozwiakowski, PhD[18] Monique Duncan[16] Laura Williams, MD, MPH[16] Julie Krop, MD[16]

[1] Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, Houston, Texas
[2] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York
[3] Section of Maternal Fetal Medicine, Women's Services, Ochsner Health Systems, New Orleans, Louisiana
[4] Department of Obstetrics and Gynecology, Duke University, Durham, North Carolina
[5] Department of Obstetrics and Gynecology, University of South Florida, Tampa, Florida
[6] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina
[7] Valley Perinatal Services, Watching Over Mothers and Babies Foundation, Tucson, Arizona
[8] Das Consulting, Guerneville, California
[9] Department of Obstetrics and Gynecology, University of Texas Medical Branch, University of Texas, Galveston, Texas
[10] Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine and The Children's Hospital of San Antonio, San Antonio, Texas

Address for correspondence Sean C. Blackwell, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, 6431 Fannin, MSB 3.286, Houston, TX 77030 (e-mail: Sean.blackwell@uth.tmc.edu).

[11] Clinical Research Prime, Idaho Falls, Idaho
[12] Department of Obstetrics and Gynecology, Bukovinian State Medical University, Chernivtsi, Ukraine
[13] Department of Obstetrics and Gynecology, Clinical Maternity Hospital # 4, Zaporizhzhya, Ukraine
[14] Department of Obstetrics and Gynecology, State Government-financed Healthcare Institution of Novosibirsk Region, Novosibirsk, Russia
[15] Department of Obstetrics and Gynecology, Saint-Petersburg Government-financed Healthcare Institution "Maternity Hospital #17," Saint-Petersburg, Russia
[16] AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[17] Formerly at AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[18] Jozwiakowski Pharma Consulting LLC, Santa Fe, New Mexico

Am J Perinatol

Abstract

Keywords

- 17-P
- 17-HPC
- 17-OHPC
- 17-hydroxypro-gesterone caproate
- progestogens
- preterm birth
- recurrent preterm birth
- spontaneous preterm birth

Background Women with a history of spontaneous preterm birth (SPTB) are at a significantly increased risk for recurrent preterm birth (PTB). To date, only one large U.S. clinical trial comparing 17-OHPC (17-α-hydroxyprogesterone caproate or "17P") to placebo has been published, and this trial was stopped early due to a large treatment benefit.

Objective This study aimed to assess whether 17-OHPC decreases recurrent PTB and neonatal morbidity in women with a prior SPTB in a singleton gestation.

Study Design This was a double-blind, placebo-controlled international trial involving women with a previous singleton SPTB (*clinicaltrials.gov*: NCT 01004029). Women were enrolled at 93 clinical centers (41 in the United States and 52 outside the United States) between $16^{0/7}$ to $20^{6/7}$ weeks in a 2:1 ratio, to receive either weekly intramuscular (IM) injections of 250 mg of 17-OHPC or an inert oil placebo; treatment was continued until delivery or 36 weeks. Co-primary outcomes were PTB < 35 weeks and a neonatal morbidity composite index. The composite included any of the following: neonatal

received
October 15, 2019
accepted after revision
October 21, 2019

DOI https://doi.org/10.1055/s-0039-3400227.
ISSN 0735-1631.

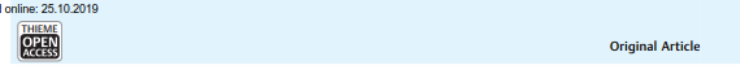
Table 2 Obstetrical outcomes

	17-OHPC $n = 1,130$	Placebo $n = 578$	RR (95% CI)
Number assessed for outcome, N1	1,113	574	0.95 (0.71–1.26)
PTB < $35^{0/7}$ wk[a]	122 (11.0)	66 (11.5)	
Spontaneous	93 (8.4)	51 (8.9)	0.93 (0.67–1.30)
Indicated	28 (2.5)	14 (2.4)	1.03 (0.55–1.93)
Number assessed for outcome, N1	1,112	572	
PTB < $37^{0/7}$ wk	257 (23.1)	125 (21.9)	1.06 (0.88–1.28)
Spontaneous	209 (18.8)	98 (17.1)	1.10 (0.88–1.36)
Indicated	46 (4.1)	26 (4.5)	0.91 (0.57–1.46)
Number assessed for outcome, N1	1,116	574	0.92 (0.60–1.42)
PTB < $32^{0/7}$ wk	54 (4.8)	30 (5.2)	
Spontaneous	38 (3.4)	22 (3.8)	0.88 (0.52–1.48)
Indicated	15 (1.3)	7 (1.2)	1.11 (0.46–2.63)
Cerclage	6 (0.5)	7 (1.2)	0.44 (0.15–1.32)
Preterm labor[b]	187(16.5)	84 (14.5)	1.14 (0.90–1.44)
Tocolysis	134 (11.9)	63 (10.9)	1.09 (0.82–1.44)
Antenatal corticosteroid therapy	105 (9.3)	61(10.6)	0.88 (0.65–1.20)
Maternal GDM	35 (3.1)	21 (3.6)	0.91 (0.54–1.54)
Preeclampsia	47 (4.2)	30 (5.2)	0.86 (0.51–1.46)
Chorioamnionitis	9 (0.8)	2 (0.3)	2.24 (0.48–10.41)
Abruption	16 (1.4)	4 (0.7)	2.04 (0.69–6.06)
Cesarean delivery	292 (25.8)	140 (24.2)	1.07 (0.90–1.27)

Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): a multicenter, international, randomized double-blinded trial. Am J Perinatol October 25, 2019

PROLONG

Published online: 25.10.2019



Original Article

17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial

Sean C. Blackwell, MD[1] Cynthia Gyamfi-Bannerman, MD, MS[2] Joseph R. Biggio Jr., MD[3] Suneet P. Chauhan, MD[1] Brenna L. Hughes, MD[4] Judette M. Louis, MD[5] Tracy A. Manuck, MD[6] Hugh S. Miller, MD[7] Anita F. Das, PhD[8] George R. Saade, MD[9] Peter Nielsen, MD[10] Jeff Baker, MD[11] Oleksandr M. Yuzko, MD, PhD[12] Galyna I. Reznichenko, MD, PhD[13] Nataliya Y. Reznichenko, MD, PhD[13] Oleg Pekarev, MD, PhD[14] Nina Tatarova, MD, PhD[15] Jennifer Gudeman, PharmD[16] Robert Birch, PhD[17] Michael J. Jozwiakowski, PhD[18] Monique Duncan[16] Laura Williams, MD, MPH[16] Julie Krop, MD[16]

[1] Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, Houston, Texas
[2] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Columbia University Irving Medical Center, New York, New York
[3] Section of Maternal Fetal Medicine, Women's Services, Ochsner Health Systems, New Orleans, Louisiana
[4] Department of Obstetrics and Gynecology, Duke University, Durham, North Carolina
[5] Department of Obstetrics and Gynecology, University of South Florida, Tampa, Florida
[6] Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina
[7] Valley Perinatal Services, Watching Over Mothers and Babies Foundation, Tucson, Arizona
[8] Das Consulting, Guerneville, California
[9] Department of Obstetrics and Gynecology, University of Texas Medical Branch, University of Texas, Galveston, Texas
[10] Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine and The Children's Hospital of San Antonio, San Antonio, Texas

Address for correspondence Sean C. Blackwell, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, 6431 Fannin, MSB 3.286, Houston, TX 77030 (e-mail: Sean.blackwell@uth.tmc.edu).

[11] Clinical Research Prime, Idaho Falls, Idaho
[12] Department of Obstetrics and Gynecology, Bukovinian State Medical University, Chernivtsi, Ukraine
[13] Department of Obstetrics and Gynecology, Clinical Maternity Hospital # 4, Zaporizhzhya, Ukraine
[14] Department of Obstetrics and Gynecology, State Government-financed Healthcare Institution of Novosibirsk Region, Novosibirsk, Russia
[15] Department of Obstetrics and Gynecology, Saint-Petersburg Government-financed Healthcare Institution "Maternity Hospital #17," Saint-Petersburg, Russia
[16] AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[17] Formerly at AMAG Pharmaceuticals, Inc, Medical Development, Waltham, Massachusetts
[18] Jozwiakowski Pharma Consulting LLC, Santa Fe, New Mexico

Am J Perinatol

Abstract

Keywords

- 17-P
- 17-HPC
- 17-OHPC
- 17-hydroxypro-gesterone caproate
- progestogens
- preterm birth
- recurrent preterm birth
- spontaneous preterm birth

Background Women with a history of spontaneous preterm birth (SPTB) are at a significantly increased risk for recurrent preterm birth (PTB). To date, only one large U.S. clinical trial comparing 17-OHPC (17-α-hydroxyprogesterone caproate or "17P") to placebo has been published, and this trial was stopped early due to a large treatment benefit.

Objective This study aimed to assess whether 17-OHPC decreases recurrent PTB and neonatal morbidity in women with a prior SPTB in a singleton gestation.

Study Design This was a double-blind, placebo-controlled international trial involving women with a previous singleton SPTB (*clinicaltrials.gov*: NCT 01004029). Women were enrolled at 93 clinical centers (41 in the United States and 52 outside the United States) between $16^{0/7}$ to $20^{6/7}$ weeks in a 2:1 ratio, to receive either weekly intramuscular (IM) injections of 250 mg of 17-OHPC or an inert oil placebo; treatment was continued until delivery or 36 weeks. Co-primary outcomes were PTB < 35 weeks and a neonatal morbidity composite index. The composite included any of the following: neonatal

received
October 15, 2019
accepted after revision
October 21, 2019

DOI https://doi.org/10.1055/s-0039-3400227.
ISSN 0735-1631.

Table 3 Neonatal outcomes—live-born neonatal population

	17-OHPC $n = 1,093$	Placebo $n = 559$	RR (95% CI)
Composite neonatal morbidity and mortality index[a]	61 (5.6)	28 (5.0)	1.12 (0.72–1.72)
Neonatal death	6 (0.5)	3 (0.5)	0.98 (0.24–3.91)
Bronchopulmonary dysplasia	6 (0.5)	1 (0.2)	3.02 (0.38–24.1)
Respiratory distress syndrome	54 (4.9)	26 (4.7)	1.06 (0.67–1.68)
Necrotizing enterocolitis	2 (0.2)	2 (0.4)	0.5 (0.07–3.40)
IVH, grade 3 or 4	2 (0.2)	1 (0.2)	0.99 (0.09–10.52)
Proven sepsis	5 (0.5)	3 (0.5)	0.84 (0.20–3.56)
NICU admission	137 (12.5)	58 (10.4)	1.21 (0.90–1.62)
Birth weight (g)	3,076.6 ± 630.0	3,080.1 ± 609.2	NA
TTN	37 (3.4)	11 (2.0)	1.72 (0.89–3.33)
Number of neonates on ventilator support/receiving supplemental oxygen	130 (11.9)	54 (9.7)	1.23 (0.91–1.67)
PDA	4 (0.4)	4 (0.7)	0.53 (0.14–2.06)
ROP	5 (0.5)	7 (1.3)	0.37 (0.12–1.16)
Neonatal LOS (for those admitted to the NICU) (d)	18.6 ± 20.4	23.3 ± 24.5	NA

Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): a multicenter, international, randomized double-blinded trial. Am J Perinatol October 25, 2019

United States Food and Drug Administration, 2019

U.S. FOOD & DRUG ADMINISTRATION

FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

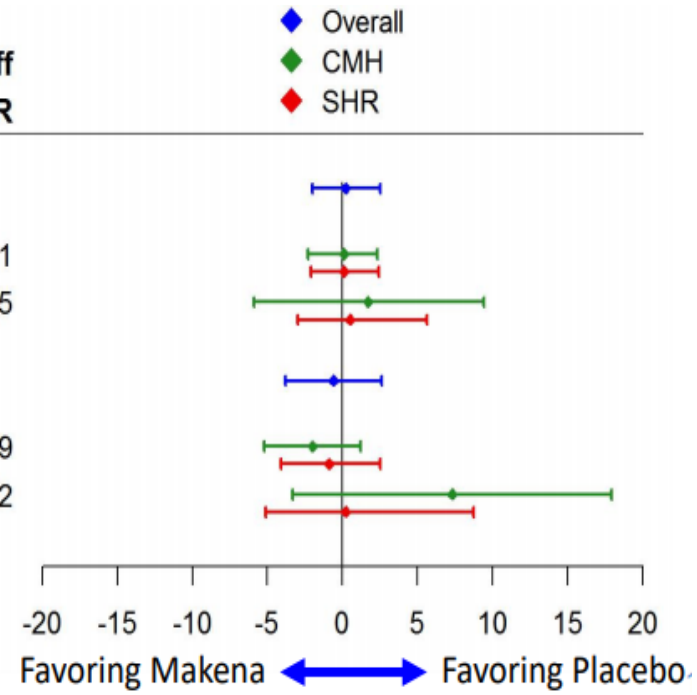
Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
1 (933, 478)	4.6	4.6	0	0.1
>1 (158, 80)	10.1	8.8	1.7	0.5
PTB<35 Weeks (%)	11.0	11.5	-0.6	
1 (949, 491)	8.4	10.4	-2.0	-0.9
>1 (164, 81)	25.6	18.5	7.3	0.2



United States Food and Drug Administration. Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting. FDA Briefing Document. NDA 021945. Hydroxyprogesterone Caproate Injection (trade name Makena). October 29, 2019.

United States Food and Drug Administration, 2019

U.S. FOOD & DRUG ADMINISTRATION

FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

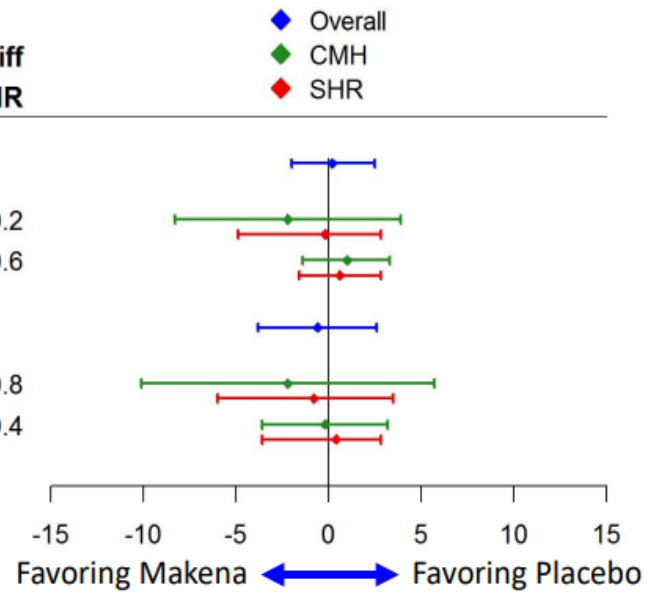
Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

Endpoint Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
US (252, 126)	7.1	9.5	-2.2	-0.2
Non_US (839, 434)	4.9	3.9	1.0	0.6
PTB<35 Weeks (%)	11.0	11.5	-0.6	
US (256, 131)	15.6	17.6	-2.2	-0.8
Non_US (857, 443)	9.6	9.7	-0.2	0.4



United States Food and Drug Administration. Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting. FDA Briefing Document. NDA 021945. Hydroxyprogesterone Caproate Injection (trade name Makena). October 29, 2019.

United States Food and Drug Administration, 2019

U.S. FOOD & DRUG ADMINISTRATION

FDA Briefing Document
NDA 021945
Hydroxyprogesterone Caproate Injection
(trade name Makena)

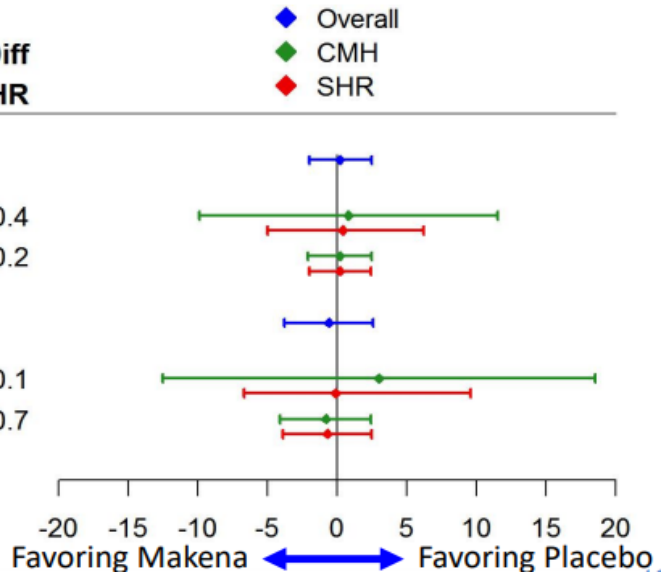
Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting
October 29, 2019
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Office of New Drugs

Division of Biometrics III
Division of Biometrics VII
Office of Biostatistics
Office of Translational Sciences

Division of Epidemiology II
Office of Surveillance and Epidemiology

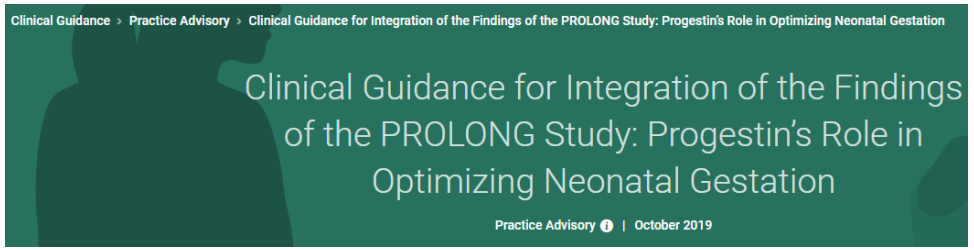
Center for Drug Evaluation and Research

Endpoint / Subgroup	Makena	Placebo	Diff CMH	Diff SHR
Neonatal Index (%)	5.4	5.2	0.2	
Black (69, 40)	8.7	7.5	0.8	0.4
Non-Black (1022, 520)	5.2	5.0	0.2	0.2
PTB<35 Weeks (%)	11.0	11.5	-0.6	
Black (72, 41)	23.6	19.5	3.0	-0.1
Non-Black (1041, 533)	10.1	10.9	-0.8	-0.7

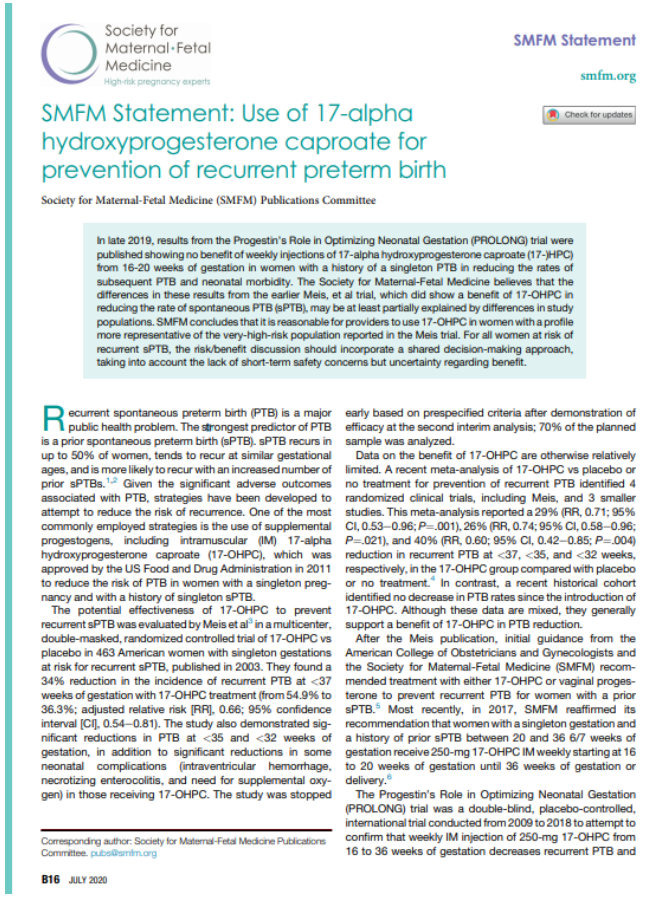


United States Food and Drug Administration. Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting. FDA Briefing Document. NDA 021945. Hydroxyprogesterone Caproate Injection (trade name Makena). October 29, 2019.

Response to 2019 FDA Advisory Committee



American College of Obstetricians and Gynecologists. Practice Advisory: Clinical guidance for integration of the findings of the PROLONG study: Progestin's Role in Optimizing Neonatal Gestation. October 25, 2019. Accessed on 18 January 2020 at: https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Clinical-guidance-for-integration-of-the-findings-of-The-PROLONG-study-Progestins-Role-in-Optimizing


Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Statement

smfm.org

Check for updates

SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

In late 2019, results from the Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial were published showing no benefit of weekly injections of 17-alpha hydroxyprogesterone caproate (17-)HPC) from 16-20 weeks of gestation in women with a history of a singleton PTB in reducing the rates of subsequent PTB and neonatal morbidity. The Society for Maternal-Fetal Medicine believes that the differences in these results from the earlier Meis, et al trial, which did show a benefit of 17-OHPC in reducing the rate of spontaneous PTB (sPTB), may be at least partially explained by differences in study populations. SMFM concludes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very-high-risk population reported in the Meis trial. For all women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit.

Recurrent spontaneous preterm birth (PTB) is a major public health problem. The strongest predictor of PTB is a prior spontaneous preterm birth (sPTB). sPTB recurs in up to 50% of women, tends to recur at similar gestational ages, and is more likely to recur with an increased number of prior sPTBs.[1,2] Given the significant adverse outcomes associated with PTB, strategies have been developed to attempt to reduce the risk of recurrence. One of the most commonly employed strategies is the use of supplemental progestogens, including intramuscular (IM) 17-alpha hydroxyprogesterone caproate (17-OHPC), which was approved by the US Food and Drug Administration in 2011 to reduce the risk of PTB in women with a singleton pregnancy and with a history of singleton sPTB.

The potential effectiveness of 17-OHPC to prevent recurrent sPTB was evaluated by Meis et al[3] in a multicenter, double-masked, randomized controlled trial of 17-OHPC vs placebo in 463 American women with singleton gestations at risk for recurrent sPTB, published in 2003. They found a 34% reduction in the incidence of recurrent PTB at <37 weeks of gestation with 17-OHPC treatment (from 54.9% to 36.3%; adjusted relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81). The study also demonstrated significant reductions in PTB at <35 and <32 weeks of gestation, in addition to significant reductions in some neonatal complications (intraventricular hemorrhage, necrotizing enterocolitis, and need for supplemental oxygen) in those receiving 17-OHPC. The study was stopped early based on prespecified criteria after demonstration of efficacy at the second interim analysis; 70% of the planned sample was analyzed.

Data on the benefit of 17-OHPC are otherwise relatively limited. A recent meta-analysis of 17-OHPC vs placebo or no treatment for prevention of recurrent PTB identified 4 randomized clinical trials, including Meis, and 3 smaller studies. This meta-analysis reported a 29% (RR, 0.71; 95% CI, 0.53–0.96; *P*=.001), 26% (RR, 0.74; 95% CI, 0.58–0.96; *P*=.021), and 40% (RR, 0.60; 95% CI, 0.42–0.85; *P*=.004) reduction in recurrent PTB at <37, <35, and <32 weeks, respectively, in the 17-OHPC group compared with placebo or no treatment.[4] In contrast, a recent historical cohort identified no decrease in PTB rates since the introduction of 17-OHPC. Although these data are mixed, they generally support a benefit of 17-OHPC in PTB reduction.

After the Meis publication, initial guidance from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either 17-OHPC or vaginal progesterone to prevent recurrent PTB for women with a prior sPTB.[5] Most recently, in 2017, SMFM reaffirmed its recommendation that women with a singleton gestation and a history of prior sPTB between 20 and 36 6/7 weeks of gestation receive 250-mg 17-OHPC IM weekly starting at 16 to 20 weeks of gestation until 36 weeks of gestation or delivery.[6]

The Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial was a double-blind, placebo-controlled, international trial conducted from 2009 to 2018 to attempt to confirm that weekly IM injection of 250-mg 17-OHPC from 16 to 36 weeks of gestation decreases recurrent PTB and

Corresponding author: Society for Maternal-Fetal Medicine Publications Committee. pubs@smfm.org

Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Am J Obstet Gynecol. 2020 Jul;223(1):B16-B18.

Response to 2019 FDA Advisory Committee

Current Commentary

OPEN

Re-examining the Meis Trial for Evidence of False-Positive Results

Baha Sibai, MD, George R. Saade, MD, and Anita F. Das, PhD

U.S. Food and Drug Administration (FDA)–approved 17α-hydroxyprogesterone caproate therapy is currently available to reduce recurrent preterm birth in the United States. This commentary reviews the original landmark Meis trial ("Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate"), which led to conditional approval of 17α-hydroxyprogesterone caproate by the FDA in 2011. The recent PROLONG (Progestin's Role in Optimizing Neonatal Gestation) trial failed to confirm the original findings. The Meis trial was rigorously designed and conducted, with highly statistically significant results that should not be undermined by the negative results of PROLONG. Given that the United States has among the highest preterm birth rates in the world and that the predominant enrollment in PROLONG was outside the United States, the results of the "old" Meis trial should not be summarily dismissed. It would be detrimental to high-risk pregnant patients to inappropriately prioritize results of PROLONG over the Maternal-Fetal Medicine Units Network's Meis trial (funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development). We assert PROLONG was underpowered, based on substantially lower observed preterm birth rates than anticipated, and therefore was a false-negative study, rather than the Meis trial being a false-positive study. Careful assessment of these two trials is critical as removal of 17α-hydroxyprogesterone caproate from the U.S. marketplace may have substantial effects on public health.

(Obstet Gynecol 2020;136:622–7)
DOI: 10.1097/AOG.0000000000003991

In 2003, Meis and colleagues from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network published their landmark trial in the *New England Journal of Medicine*.[1] This was the first rigorous, placebo-controlled trial to demonstrate an intervention reduced preterm birth in women with a history of spontaneous preterm birth. This finding expanded on the results of a meta-analysis of five randomized trials that demonstrated a 42% reduction in the rate of recurrent preterm birth with 17α-hydroxyprogesterone caproate.[2]

The Meis trial was heralded as a major advance in the field of obstetrics and led to U.S. Food and Drug Administration (FDA) approval of Makena in 2011. A requirement by the FDA was the initiation of a second confirmatory trial, known as PROLONG (Progestin's Role in Optimizing Neonatal Gestation), which began in 2009. PROLONG, conducted largely outside the United States, failed to confirm the benefit of 17α-hydroxyprogesterone caproate in women with the same eligibility criteria as the Meis trial.[3] In October 2019, an FDA Advisory Committee voted 9–7 to recommend the FDA pursue withdrawal of 17α-hydroxyprogesterone caproate. Notably, this action would apply to the original Makena intramuscular formulation, any FDA-approved generic equivalents,

From the Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, Houston, and the Department of Obstetrics and Gynecology, University of Texas Medical Branch at Galveston, Galveston, Texas; and Das Consulting, Guerneville, California.

The authors thank AMAG Pharmaceuticals Inc employees Jennifer Gudeman and Paula Moon-Massat for reviewing the manuscript for accuracy regarding the FDA application and data.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Baha Sibai, MD, Department of Obstetrics, Gynecology, and Reproductive Sciences, McGovern Medical School-UTHealth, Houston, TX; email: baha.m.sibai@uth.tmc.edu.

Financial Disclosure
Baha M. Sibai disclosed that he received payments from AMAG for travel reimbursement as well as consultation fees for the FDA Advisory Committee meeting. George R. Saade disclosed that he received payments from AMAG for travel reimbursement as well as advisory board and consultation fees. Anita F. Das disclosed receiving funds from AMAG Pharmaceuticals and that she is a consultant for Hologic.

ISSN: 0029-7844/20

Sibai B, Saade GR, Das AF. Re-examining the Meis Trial for Evidence of False-Positive Results. Obstet Gynecol 2020;136:622-7.

Current Commentary

Accelerated Approval of 17α-Hydroxyprogesterone Caproate

A Cautionary Tale

Bethany J. Godlewski, PhD, Lily I. Sobolik, MPP, Valerie J. King, MD, MPH, and Curtis S. Harrod, PhD, MPH

Before 2011, 17α-hydroxyprogesterone caproate (17P) was used to prevent recurrent preterm birth in women with singleton pregnancies and was compounded at a low cost (~$15 per injection). In 2011, the U.S. Food and Drug Administration (FDA) approved a commercial version of 17P (trade name "Makena") through their Accelerated Approval Program, and the price of 17P subsequently increased by nearly 100-fold. This approval was largely based on a methodologically limited, placebo-controlled trial, which found that although 17P significantly reduced preterm births, the placebo group had significantly more participants with a history of preterm birth, potentially confounding the results. The FDA required a confirmatory trial for continued approval that demonstrated clinical benefit. Eight years after accelerated approval, the confirmatory trial, PROLONG (Progestin's Role in Optimizing Neonatal Gestation), found no evidence of an effect of Makena for reducing recurrent preterm birth or perinatal mortality. Trial completion triggered an automatic review of Makena by an advisory committee, which voted 9–7 to recommend revoking approval of Makena for preterm birth. Although the FDA created the Accelerated Approval Program to introduce therapies for serious conditions that lacked treatment options, Makena is an example of the limitations of this program. We encourage the FDA to re-evaluate their program and consider improvements, such as shorter timeframes to complete confirmatory trials, potentially revoking approval if the studies are not completed within a predefined timeframe, and to hold manufacturers responsible, in part, for the costs of therapy if they cannot prove a clinical benefit.

(Obstet Gynecol 2020;135:1207–13)
DOI: 10.1097/AOG.0000000000003787

Preterm birth (20–37 weeks of gestation) complicates 1 in 8–10 pregnancies, is associated with 85% of perinatal morbidity and mortality, and disproportionately affects racial and ethnic minorities.[1,2] More than half of all preterm births are spontaneous.[3] These factors make it clear that we need evidence-based treatments to mitigate these short-term and long-term health consequences. However, there are few treatment options for preterm birth and none of the U.S. Food and Drug Administration (FDA)–approved treatments have been shown to effectively reduce perinatal mortality.[4,5]

Similar to most complex conditions, preterm birth includes modifiable and nonmodifiable risk factors and risk markers such as births to teens or young mothers, smoking, race or ethnicity, short cervical length, and a previous preterm birth.[1,2] Because of the occurrence and severity of preterm birth, patients, health care providers, and insurers desire treatment options to reduce preterm birth.

In late 2018, a collaborative of state Medicaid agencies participating in the Medicaid Evidence-based Decisions Project, housed at the Center for Evidence-based Policy at Oregon Health & Science

From the Center for Evidence-based Policy at Oregon Health & Science University, Portland, Oregon.

The evidence review that inspired the development of this manuscript was funded by the Medicaid Evidence-based Decisions Project. This manuscript was written in-kind: it refers to knowledge gained in the course of employee duties, but was written outside of the role and remuneration of work at the Center for Evidence-based Policy.

Each author has confirmed compliance with the journal's requirements for authorship.

Corresponding author: Curtis S. Harrod, PhD, MPH, Center for Evidence-based Policy, Oregon Health & Science University, Portland, OR; email: harrodc@ohsu.edu.

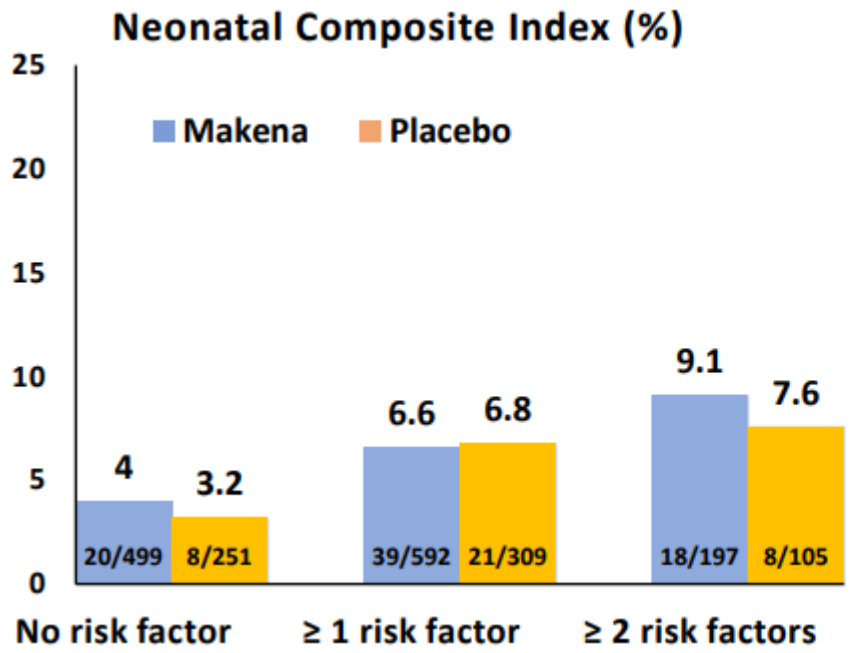
Financial Disclosure
All authors are employees of the Center for Evidence-based Policy at Oregon Health & Science University. The authors did the evidence review on 17P for states involved in a collaborative of state Medicaid programs and were paid, as part of their regular salaries, for the production of that report. The report is publicly available, and the collaborative has given permission for its use in this commentary.

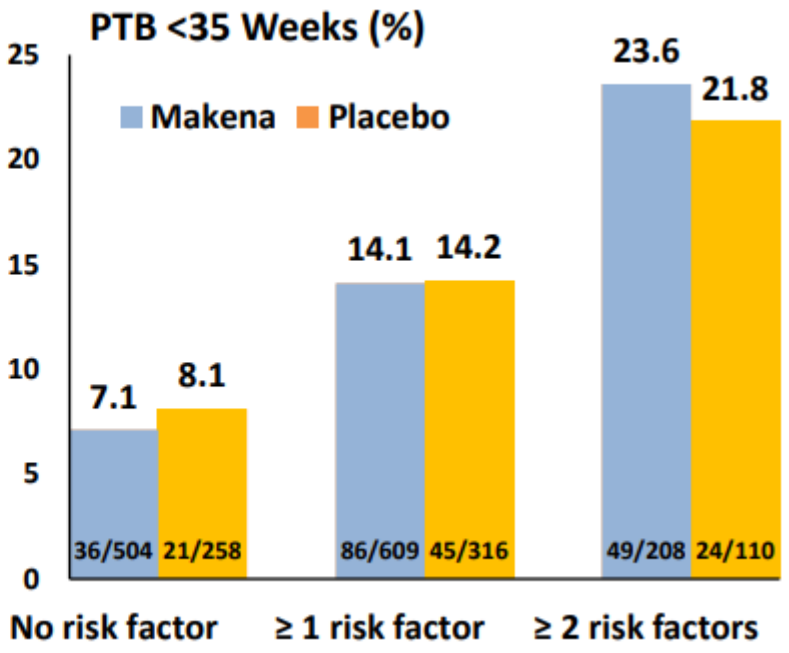
ISSN: 0029-7844/20

Godlewski BJ, Sobolik LI, King VJ, et al. Accelerated Approval of 17α-Hydroxyprogesterone Caproate: A Cautionary Tale. Obstet Gynecol. 2020 May;135(5):1207-13.

UTSouthwestern Medical Center

FDA post hoc analysis of Trial 003 [PROLONG Trial]





Five factors noted to different between the MFMU Network and PROLONG Trials:
(1) black race
(2) history of more than one previous preterm birth
(3) single or without partner
(4) substance use during pregnancy
(5) less or equal 12 years of formal education

United States Food and Drug Administration. Event Materials. FDA Presentations for the October 29, 2019 Meeting of the Bone, Reproductive, and Urologic Drugs Advisory Committee. Accessed on 23 Aug 2020: https://www.fda.gov/media/132431/download

Regulatory withdrawal: A case example

- Important issue in healthcare
- Initial trial suggested benefit
- Accelerated approval granted
- Confirmatory trial negative
- US FDA Advisory Committee recommends withdrawal

Regulatory withdrawal: A case example

- Important issue in healthcare
- Initial trial suggested benefit
- Accelerated approval granted
- Confirmatory trial negative
- US FDA Advisory Committee recommends withdrawal

Avastin®

Vitry et al. Journal of Pharmaceutical Policy and Practice (2015) 8:25
DOI 10.1186/s40545-015-0046-2

JOURNAL OF PHARMACEUTICAL POLICY AND PRACTICE

RESEARCH Open Access

Regulatory withdrawal of medicines marketed with uncertain benefits: the bevacizumab case study

Agnes Vitry[1*], Tuan Nguyen[1], Vikky Entwistle[2] and Elizabeth Roughead[1]

Abstract

Background: Withdrawal of conditional regulatory approval or subsidization of new medicines when subsequent evidence does not confirm early trial results may not be well understood or accepted by the public.

Objectives: We present a case study of the US Food and Drug Administration (FDA)'s decision to withdraw the indication of bevacizumab for the treatment of advanced breast cancer and include an analysis of the reactions of stakeholders with a view to identifying opportunities for improving risk management for new medicines with conditional approval or funding.

Methods: We drew on a range of information sources, including FDA documents, medical journals and media reports, to describe the evidentiary basis of the FDA decisions. We analysed the reactions and perspectives of the stakeholders.

Results: In 2008 bevacizumab was granted conditional approval for treatment of advanced breast cancer by the FDA pending submission of supplementary satisfactory evidence. In 2011 the FDA decision to withdraw the indication was met with a hostile reaction from many clinicians and cancer survivors. There were different interpretations of the therapeutic value of bevacizumab with strong beliefs among cancer survivors that the medicine was effective and potential harm was manageable. High expectations of the public may have been encouraged by overly positive media reports and limited understanding by the public of the complexity of the scientific evaluation of new medicines and of the regulatory processes.

Conclusions: Improving understanding and acceptance of approval or coverage schemes conditional to evidence development may require the development of risk management plans by regulatory and funding institutions. They may include a range of strategies such as requirements for formal patient acknowledgment of the conditional availability of the medicine, 'black-triangle' equivalent labels that identify full approval is based on pending evidence, and ongoing communication with the media, public and health professionals.

Keywords: Pharmaceutical policy, Managed entry agreement, Medicine subsidization, Coverage with evidence development

Introduction

In the United States, the Food and Drug Administration (FDA) has implemented an accelerated approval program for medicines that appear to provide a benefit for serious or life-threatening illnesses lacking satisfactory treatments [1]. Under this program, medicines are given a conditional approval based on clinical trial data that suggest efficacy but are not sufficient to permit full approval. Full approval depends on subsequent confirmatory clinical trials. Some countries with national public health insurance systems, including Australia, Canada, Italy and the United Kingdom, have introduced similar 'coverage-with-evidence development' schemes in which approved medicines may be subsidised pending the later submission of satisfactory research data [2].

These new schemes are attractive for policymakers as they may temporarily resolve tensions between the objectives of (a) maintaining efficacy, safety and cost-

* Correspondence: agnes.vitry@unisa.edu.au
[1]Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, GPO Box 2471, Adelaide, SA 5001, Australia
Full list of author information is available at the end of the article

Vitry A, et al. J Pharm Policy Pract. 2015;8:25.

In 2020…

CDER proposes withdrawal of approval fo Makena

Share | Tweet | Linkedin | Email | Print

[10/5/2020] Today, the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) proposed that Makena (hydroxyprogesterone caproate injection) be withdrawn from the market because the required postmarket study failed to verify clinical benefit and we have concluded that the available evidence does not show Makena is effective for its approved use.

Makena received accelerated approval in 2011 to reduce the risk of preterm birth in women who previously had a spontaneous (unexplained) preterm birth, which is delivery of a baby before 37 weeks. As part of this accelerated approval, the company was required to conduct a clinical trial to confirm the drug provided clinical benefit to newborns. A drug that prevents preterm birth is helpful if it ultimately improves the babies' health. The required confirmatory trial failed to show that Makena is effective for improving the health of babies born to women with a history of unexplained preterm birth. We also determined that the available evidence does not show that Makena reduces the risk of preterm birth. Therefore, CDER has proposed that Makena be withdrawn from the market and has issued a notice of opportunity for a hearing (NOOH) to the application holder of Makena, AMAG Pharmaceuticals. FDA also sent the NOOH to the application holders for the approved generics to Makena for an opportunity to comment.

FDA CDER. 5 Oct 2020

In 2020…

News & Analysis

Medical News & Perspectives

Confirmatory Trial for Drug to Prevent Preterm Birth Finds No Benefit, So Why Is It Still Prescribed?

Rita Rubin, MA

Preterm birth represents a major US public health problem, with 1 in 10 neonates born before 37 weeks' gestation in 2018, placing them at a greater risk of death and disability.

So it's not surprising that pregnant women who've already spontaneously delivered a baby preterm would be eager for a treatment that promises to help them get closer to term. Same goes for their physicians.

For nearly a decade, that treatment has been Makena (hydroxyprogesterone caproate), a long-acting form of a naturally occurring progesterone. Makena was approved in February 2011 under accelerated approval regulations of the US Food and Drug Administration (FDA), which allow promising drugs to enter the market based on a surrogate end point benefit—in this case, reducing the risk of delivery before 37 weeks—that is likely to predict a clinical benefit.

Fast-track approvals are granted on the condition that drugs' sponsors conduct additional studies to confirm a clinical benefit, such as reduced neonatal morbidity and mortality. But what happens when the confirmatory study fails to confirm the effectiveness of a drug that has become the standard of care?

That question is dogging Makena. In March 2019, AMAG Pharmaceuticals, for whom Makena was its best seller before sales dropped in 2019, announced that the confirmatory trial, called PROLONG (Progestin's Role in Optimizing Neonatal Gestation), found that the drug was no more effective than a placebo.

Four days after publication of the PROLONG results in late October, the FDA convened an advisory committee meeting to help it decide whether to keep Makena, injected weekly beginning at 16 through 20 weeks' gestation, on the market. The panel evaluated comments from women who credited Makena for their full-term deliveries and AMAG representatives' explanations of why PROLONG's findings differed substantially from the 2003 trial on which Makena's approval was based.

After weighing the evidence, the panelists discussed and voted on questions posed by the FDA. They voted unanimously that the PROLONG trial did not "verify the clinical benefit of Makena on neonatal outcomes." Of the 16 panelists, 13 voted no and only 3 voted yes when asked whether they thought PROLONG and the drug's original trial provided "substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth."

However, the vote on whether to withdraw Makena was much closer. Nine committee members said it should be withdrawn and 7—including 5 of the 6 practicing obstetricians on the panel—said it should remain on the market, under the condition that AMAG conduct another confirmatory trial. Whether such a trial is feasible isn't clear, though. Several panelists noted that pregnant women who'd already delivered preterm would be unlikely to enroll in a study in which they might get a placebo instead of the only medication indicated for reducing the risk of another preterm birth. None of the panelists voted for a third option: leaving Makena on the market without requiring a new confirmatory trial.

"[W]e are committed to working with the FDA to identify feasible ways to generate additional efficacy data on Makena while retaining current access to the therapy for at-risk pregnant women," PROLONG coauthor Julie Krop, MD, AMAG's chief medical officer until her March 31 departure, said in a prepared statement after the advisory committee vote.

For now, Makena remains on the market, and the Society for Maternal-Fetal Medicine (SMFM) and the American College of Obstetricians and Gynecologists (ACOG)—the 2 main professional organizations of physicians who care for women at risk of delivering preterm—continue to recommend that members prescribe it to patients for whom it is indicated.

At least a few of the groups' members have questioned whether AMAG's role as a major donor to SMFM and ACOG (it's also a March of Dimes "corporate partner") has affected the organizations' judgment when it comes to Makena. And at least

Bad Optics?

Over the years, AMAG Pharmaceuticals has provided financial support to the March of Dimes, ACOG, and SMFM, none of which has yet provided guidance that reflects the PROLONG trial's findings of no benefit. Whether that's because they get AMAG funding isn't known—Blackwell emphasized that no one on the SMFM

Rubin R. Confirmatory Trial for Drug to Prevent Preterm Birth Finds No Benefit, So Why Is It Still Prescribed? JAMA. 2020

In 2021…

A chronicle of the 17-alpha hydroxyprogesterone caproate story to prevent recurrent preterm birth

David B. Nelson, MD; Donald D. McIntire, PhD; Kenneth J. Leveno, MD†

Check for updates

Clinical Opinion

Preterm birth (PTB) is a substantial public health concern. In 2019, the US PTB rate was 10.23%, which is the fifth straight year of increase in this rate.[1] Moreover, PTB accounts for approximately 1 in 6 infant deaths, and surviving children often suffer developmental delay or long-term neurologic impairment.[2-5] Complications of PTB remain one of the leading causes of death globally in children younger than 5 years, accounting for more than one-third of deaths among neonates.[2,4] Spontaneous PTB (sPTB) represents a syndrome with multiple causes; however, one of the strongest risk factors of recurrence is a history of PTB, which increases the risk by 1.5- to 2-fold.[2] In addition, the number of previous PTBs and the gestational age of previous PTBs impact the recurrence risk.[2] Although the burden of PTB is clear, identifying strategies to reduce PTB has been challenging.

On October 29, 2019, a US Food and Drug Administration (FDA) advisory committee voted 9 to 7 to withdraw the approval of 17-alpha hydroxyprogesterone caproate (17OHP-C) for preventing recurrent PTB.[5] The original FDA approval was a result of the accelerated approval process for orphan drugs and

From the Department of Obstetrics and Gynecology, The University of Texas Southwestern Medical Center, Dallas, TX.

†Deceased.

Received Jan. 29, 2020; revised Sept. 18, 2020; accepted Sept. 21, 2020.

The authors report no conflict of interest.

Corresponding author: David B. Nelson, MD.
davidb.nelson@utsouthwestern.edu

0002-9378/$36.00

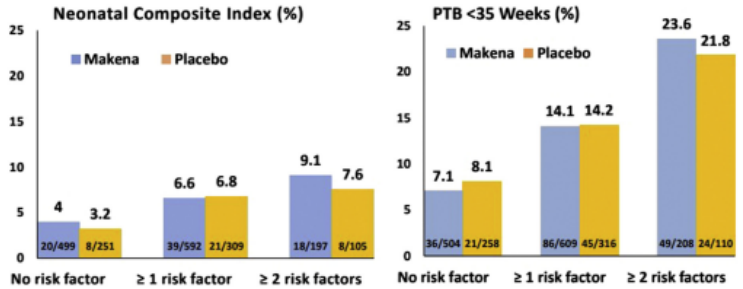
https://doi.org/10.1016/j.ajog.2020.09.045

Click Supplemental Materials under article title in Contents at

Preterm birth is a substantial public health concern. In 2019, the US preterm birth rate was 10.23%, which is the fifth straight year of increase in this rate. Moreover, preterm birth accounts for approximately 1 in 6 infant deaths, and surviving children often suffer developmental delay or long-term neurologic impairment. Although the burden of preterm birth is clear, identifying strategies to reduce preterm birth has been challenging. On October 29, 2019, a US Food and Drug Administration advisory committee voted 9 vs 7 to withdraw interim accelerated approval of 17-alpha hydroxyprogesterone caproate for preventing recurrent preterm birth because the called for a confirmatory trial, known as the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial, was not confirmatory. The Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial included subjects enrolled in the United States and Canada to ensure that at least 10% of patients would be from North America; however, this trial took 9 years to complete and did not demonstrate significant treatment effects in the 2 primary outcomes of interest. Delivery before 35 weeks' gestation occurred in 122 of 1130 women (11%) given 17-alpha hydroxyprogesterone caproate compared with 66 of 578 women (11.5%) given placebo (relative risk, 0.95; 95% confidence interval, 0.71–1.26; *P*=.72). Similarly, the coprimary outcome neonatal composite index occurred in 61 of 1093 women (5.6%) given 17-alpha hydroxyprogesterone caproate compared with 28 of 559 women (5.0%) given placebo (relative risk, 1.12; 95% confidence interval, 0.68–1.61; *P*=.73). There was also a lack of efficacy for 17-alpha hydroxyprogesterone caproate treatment in the analysis of a variety of secondary outcomes. Like the Maternal-Fetal Medicine Units Network trial, the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial was also flawed. Importantly, the Maternal-Fetal Medicine Unit Network trial was the sole justification for treating women in the United States with 17-alpha hydroxyprogesterone caproate for nearly 2 decades. Currently, despite more than half a century, 17-alpha hydroxyprogesterone caproate still has not been found to be clearly effective. In this context, how does the advising physician dependent on scientific evidence advise a patient that 17-alpha hydroxyprogesterone caproate is effective when the evidence to support this advice has repeatedly been found to be inadequate? This clinical opinion is a critical appraisal of the 2 randomized trials examining the efficacy of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth and a chronicle of events in the regulatory process of drug approval to help answer this question. With this examination, these events illustrate the complexity of pharmaceutical regulations in the era of accelerated Food and Drug Administration approval and characterize the financial impact and influence in medicine. In this report, we also emphasize the value of observational studies in contemporary practice and identify other examples in medicine where accelerated Food and Drug Administration approval has been withdrawn. Importantly, the themes of the 17-alpha hydroxyprogesterone caproate story are not limited to obstetrics. It can also serve as a microcosm of issues within the US healthcare system, which ultimately contributes to the high cost of healthcare. In our opinion, the answer to the question is clear—the facts speak for themselves—and we believe 17-alpha hydroxyprogesterone caproate should not be endorsed for use to prevent recurrent preterm birth in the United States.

Key words: 17-alpha hydroxyprogesterone caproate, accelerated approval, evidence-based medicine, Food and Drug Administration, healthcare cost, pharmaceutical industry, pregnancy, preterm labor, progesterone, progestin, progestogen, randomized clinical trial, real-world evidence, regulatory process, subgroup analysis, withdrawal

FIGURE 4
The PROLONG trial examining 5 demographic and baseline characteristics



US FDA subgroup analysis of coprimary endpoints, neonatal index, and PTB at <35 weeks' gestation for the PROLONG trial examining 5 demographic and baseline characteristics noted to be different from the MFMU Network trial: black race, history of more than 1 previous PTB, single or without a partner, substance use during pregnancy, and ≤12 years of formal education. The 3 groups examined in this posthoc composite risk profile analysis were those without any of the 5 factors (no risk factor), those with at least 1 factor (≥1 risk factor), and those with at least 2 factors (≥2 risk factors). Makena represents 17OHP-C. Adapted from the US FDA.[35]

17OHP-C, 17-alpha hydroxyprogesterone caproate; *FDA*, Food and Drug Administration; *MFMU*, Maternal-Fetal Medicine Units; *PROLONG*, Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery; *PTB*, preterm birth; *sPTB*, spontaneous preterm birth.

Nelson. The 17-alpha hydroxyprogesterone caproate story to prevent recurrent preterm birth. Am J Obstet Gynecol 2021.

$1.327 billion.[24–27,52–54] AMAG, the current owner of 17OHP-C, now labeled Makena, had annual Makena revenue totaling $387 million and $322 million for 2017 and 2018, respectively.[55,56] Because 17OHP-C has generated hundreds of millions of dollars for pharmaceutical corporations, it is problematic that 17OHP-C has been at the center of controversy for price gouging.[57] Fried and colleagues,[58] for example, reported that the branded drug cost of 17OHP-C was 5200% more than the equivalent compounded drug ($10,917 vs $206 for average drug cost per pregnancy).

The financial consequences of drug pricing can be found in the national healthcare expenditures shared by all in the United States.[58,59] The United States spends twice as much per capita on healthcare but performs less well on many health outcomes used to compare high-income countries.[58,59] Drug prices have been recognized as a major driver to this cost.[58–62] For example, Papanicolas and colleagues[60] recently reported that total US pharmaceutical expenditures are $1443 per capita compared with a mean of $749 in 11 other high-income countries. This finding is consistent with the US Department of Health and Human Services that showed that 16.7% of total personal healthcare spending ($457 billion in 2015) was attributed to pharmaceuticals.[63] No other category of spending accounts for as much of the cost as does pharmaceuticals.[63]

Is Academic Medicine for Sale?

There is another dimension to the 17OHP-C corporate story. This has to do with the optics of corporate financial sponsorship in medicine. Such optics include donations made by AMAG in support of professional organizations and payment for consultation of individual physicians.[54,64] This support includes helping to underwrite annual meetings, educational grants, and research grants totaling $300,000 each year for the past 4 years.[64–70] To be clear, our national organizations are not alone. This issue can be found locally as our own organization has received such support for the sponsorship of meetings.[69] To be sure, corporate sponsorships of monetary gifts in American medicine are accepted to be legitimate and do not necessarily portend a conflict of interest. Moreover, individuals are expected to disclose any financial involvement that could represent potential conflicts of interest when submitting manuscripts for publication. For example, Drs Sibai, Saade, and Das reported such financial disclosures for AMAG in their recently published commentary.[34] Furthermore, the optics of corporate donations raise concerns of financial sponsorship influencing medicine.[70] Rita Rubin,[70] a medical writer for the *Journal of American Medical Association*, recently published an article summarizing these issues titled, "Confirmatory trial for drug to prevent preterm birth finds no benefit, so why is it still prescribed?" In fact, this report outlined many of the issues surrounding

Nelson et al. AJOG 2021

UTSouthwestern Medical Center

In 2021…EPPPIC

Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials

The EPPPIC Group*

Summary

Background Preterm birth is a global health priority. Using a progestogen during high-risk pregnancy could reduce preterm birth and adverse neonatal outcomes.

Methods We did a systematic review of randomised trials comparing vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control, or with each other, in asymptomatic women at risk of preterm birth. We identified published and unpublished trials that completed primary data collection before July 30, 2016, (12 months before data collection began), by searching MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database, and relevant trial registers between inception and July 30, 2019. Trials of progestogen to prevent early miscarriage or immediately-threatened preterm birth were excluded. Individual participant data were requested from investigators of eligible trials. Outcomes included preterm birth, early preterm birth, and mid-trimester birth. Adverse neonatal sequelae associated with early births were assessed using a composite of serious neonatal complications, and individually. Adverse maternal outcomes were investigated as a composite and individually. Individual participant data were checked and risk of bias assessed independently by two researchers. Primary meta-analyses used one-stage generalised linear mixed models that incorporated random effects to allow for heterogeneity across trials. This meta-analysis is registered with PROSPERO, CRD42017068299.

Findings Initial searches identified 47 eligible trials. Individual participant data were available for 30 of these trials. An additional trial was later included in a targeted update. Data were therefore available from a total of 31 trials (11 644 women and 16 185 offspring). Trials in singleton pregnancies included mostly women with previous spontaneous preterm birth or short cervix. Preterm birth before 34 weeks was reduced in such women who received vaginal progesterone (nine trials, 3769 women; relative risk [RR] 0·78, 95% CI 0·68–0·90), 17-OHPC (five trials, 3053 women; 0·83, 0·68–1·01), and oral progesterone (two trials, 181 women; 0·60, 0·40–0·90). Results for other birth and neonatal outcomes were consistently favourable, but less certain. A possible increase in maternal complications was suggested, but this was uncertain. We identified no consistent evidence of treatment interaction with any participant characteristics examined, although analyses within subpopulations questioned efficacy in women who did not have a short cervix. Trials in multifetal pregnancies mostly included women without additional risk factors. For twins, vaginal progesterone did not reduce preterm birth before 34 weeks (eight trials, 2046 women: RR 1·01, 95% CI 0·84–1·20) nor did 17-OHPC for twins or triplets (eight trials, 2253 women: 1·04, 0·92–1·18). Preterm premature rupture of membranes was increased with 17-OHPC exposure in multifetal gestations (rupture <34 weeks RR 1·59, 95% CI 1·15–2·22), but we found no consistent evidence of benefit or harm for other outcomes with either vaginal progesterone or 17-OHPC.

Interpretation Vaginal progesterone and 17-OHPC both reduced birth before 34 weeks' gestation in high-risk singleton pregnancies. Given increased underlying risk, absolute risk reduction is greater for women with a short cervix, hence treatment might be most useful for these women. Evidence for oral progesterone is insufficient to support its use. Shared decision making with woman with high-risk singleton pregnancies should discuss an individual's risk, potential benefits, harms and practicalities of intervention. Treatment of unselected multifetal pregnancies with a progestogen is not supported by the evidence.

Funding Patient-Centered Outcomes Research Institute.

Lancet 2021; 397: 1183–94

See **Comment** page 1158

*Members of the EPPPIC group are listed at the end of the manuscript

Correspondence to:
Prof Lesley A Stewart, Centre for Reviews and Dissemination, University of York, York YO10 5DD, UK
lesley.stewart@york.ac.uk

Introduction

Preterm birth is the most common cause of neonatal morbidity and mortality globally, with rates ranging from 5% in Europe to 18% in Africa.[1] Infants born prematurely are at greater risk of difficulties at birth, health problems during infancy, and death during their first year.[2] They are more likely to have long-term health problems such as cerebral palsy, epilepsy, cognitive disability, blindness, or hearing loss. Preterm birth can have economic consequences for families, and for payers and purchasers

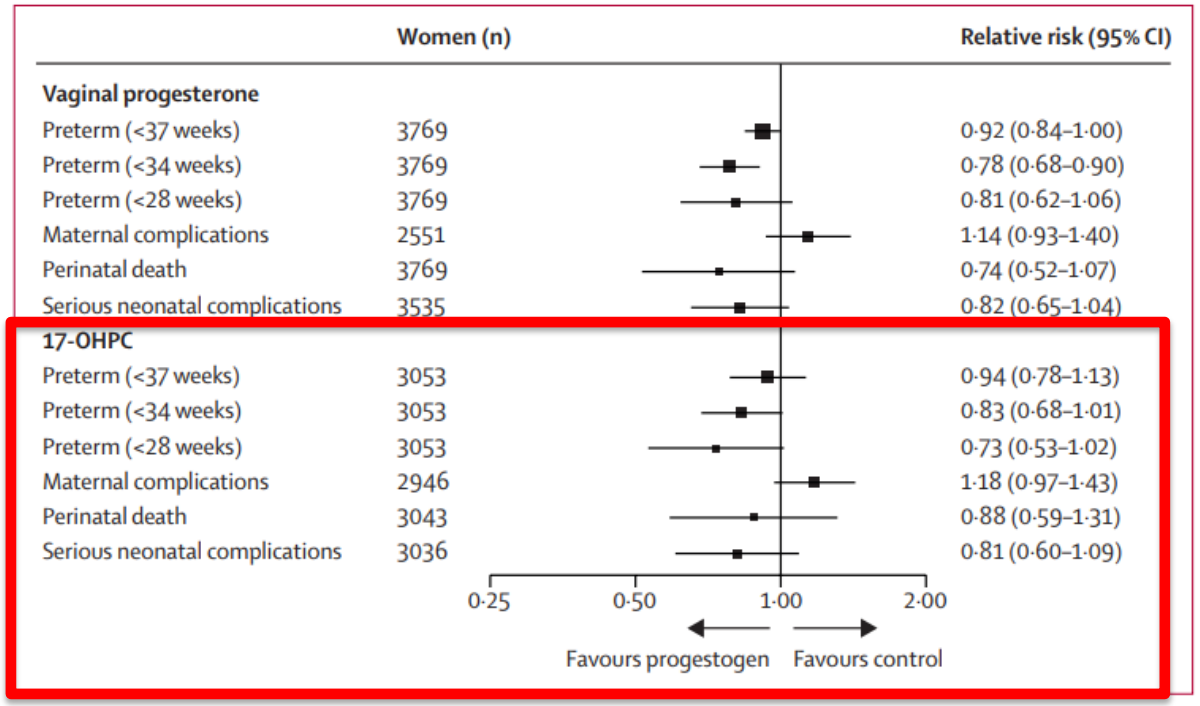
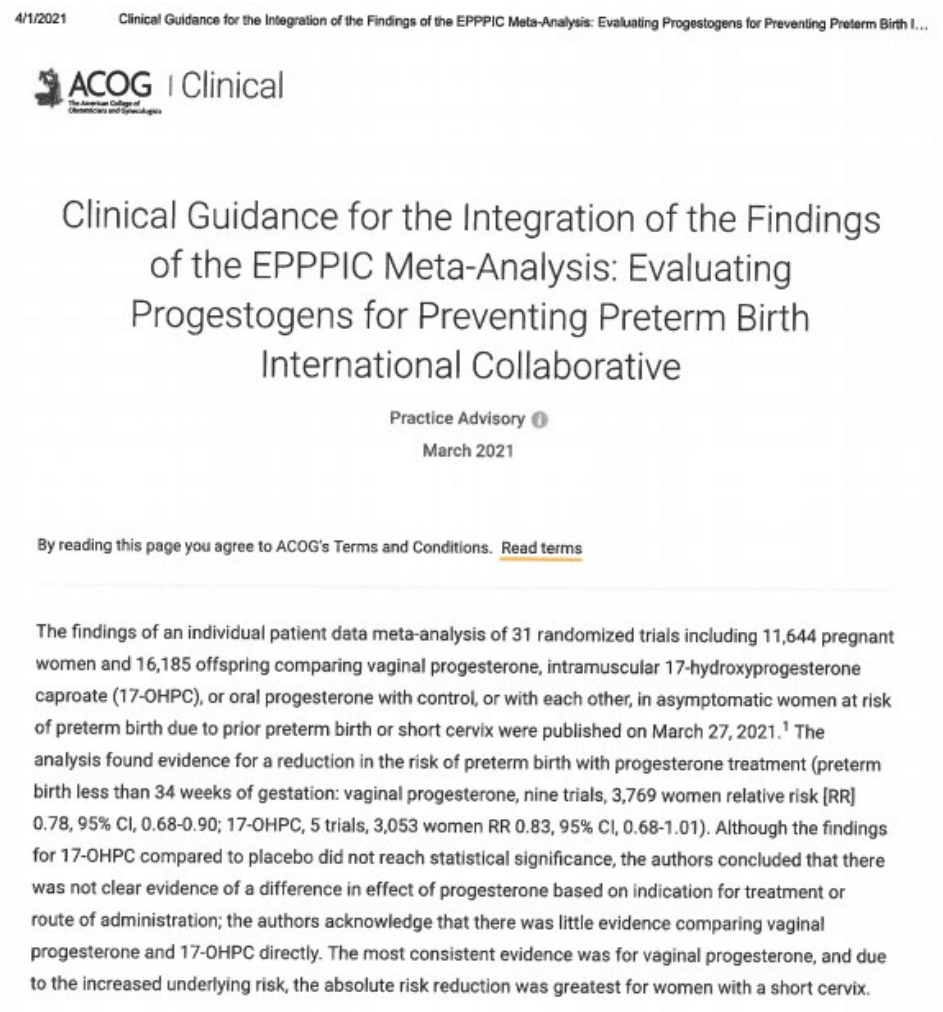


Figure 2: **Main outcomes in singleton pregnancies for vaginal progesterone and 17-OHPC trials**
17-OHPC=17-hydroxyprogesterone caproate. For vaginal progesterone: preterm birth <37 weeks number of events (n)=661, control n=705; preterm birth <34 weeks n=276, control n=343; preterm birth <28 weeks n=92, control n=111; maternal complications n=186, control n=171; perinatal death n=49, control n=64; serious neonatal complications n=119, control n=140. For 17-OHPC: preterm birth <37 weeks n=510, control n=330; preterm birth <34 weeks n=206, control n=158; preterm birth <28 weeks n=77, control n= 66; maternal complications n=285, control n=178; perinatal death n=57, control n=40; serious neonatal complications n=95, control n=75.

EPPPIC. Lancet. 27 Mar 2021

In 2021…ACOG responds to EPPPIC



4/1/2021 Clinical Guidance for the Integration of the Findings of the EPPPIC Meta-Analysis: Evaluating Progestogens for Preventing Preterm Birth I…

ACOG | Clinical

Clinical Guidance for the Integration of the Findings of the EPPPIC Meta-Analysis: Evaluating Progestogens for Preventing Preterm Birth International Collaborative

Practice Advisory

March 2021

The findings of an individual patient data meta-analysis of 31 randomized trials including 11,644 pregnant women and 16,185 offspring comparing vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control, or with each other, in asymptomatic women at risk of preterm birth due to prior preterm birth or short cervix were published on March 27, 2021.[1] The analysis found evidence for a reduction in the risk of preterm birth with progesterone treatment (preterm birth less than 34 weeks of gestation: vaginal progesterone, nine trials, 3,769 women relative risk [RR] 0.78, 95% CI, 0.68-0.90; 17-OHPC, 5 trials, 3,053 women RR 0.83, 95% CI, 0.68-1.01). Although the findings for 17-OHPC compared to placebo did not reach statistical significance, the authors concluded that there was not clear evidence of a difference in effect of progesterone based on indication for treatment or route of administration; the authors acknowledge that there was little evidence comparing vaginal progesterone and 17-OHPC directly. The most consistent evidence was for vaginal progesterone, and due to the increased underlying risk, the absolute risk reduction was greatest for women with a short cervix.

ACOG Practice Advisory. Mar 2021

In 2021…CDER responds to EPPPIC

Safety and Availability / CDER perspective on recently published results of EPPPIC meta-analysis

CDER perspective on recently published results of EPPPIC meta-analysis

Share Tweet Linkedin Email Print

Drug Safety and Availability

- Information about Nitrosamine Impurities in Medications
- Drug Alerts and Statements
- Medication Guides
- Drug Safety Communications

Drug Shortages

FDA Drug Safety Podcasts

Information by Drug Class

[3/26/2021] The U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) is aware of the recently published EPPPIC meta-analysis reporting the efficacy of various progestogens, with various routes of administration (vaginal progesterone, oral progesterone, intramuscular hydroxyprogesterone caproate [HPC]) to reduce the risk of pre-term birth (PTB) in at-risk women with singleton or multifetal pregnancies. CDER's recent proposal to withdraw the accelerated approval of Makena (HPC) was based upon a large randomized trial that failed to confirm the benefit of this drug to newborns or reduce the risk of PTB. In making the decision to propose Makena's withdrawal, CDER also reviewed results from prior studies of progestins (HPC and other similar drugs) for PTB, including studies relevant to Makena that are included in the EPPPIC meta-analysis. Therefore, the publication of the EPPPIC meta-analysis does not change CDER's proposal to withdraw the approval of Makena.

The EPPPIC meta-analysis is a patient level meta-analysis of 31 randomized, controlled trials evaluating the effect of various progestogens in reducing the risk of PTB. EPPPIC included 15 trials evaluating HPC; only five of these evaluated singleton pregnancies (the indicated population for Makena) and compared HPC with placebo.

Content current as of:
03/26/2021

Regulated Product(s)
Drugs

Topic(s)
Safety - Issues, Errors, and Problems

FDA CDER. 26 Mar 2021

In 2022…another letter to the editor (#6 letter we had received!)

A chronicle of the 17-alpha hydroxyprogesterone caproate story to prevent recurrent preterm birth

David B. Nelson, MD; Donald D. McIntire, PhD; Kenneth J. Leveno, MD†

Clinical Opinion

Preterm birth (PTB) is a substantial public health concern. In 2019, the US PTB rate was 10.23%, which is the fifth straight year of increase in this rate.[1] Moreover, PTB accounts for approximately 1 in 6 infant deaths, and surviving children often suffer developmental delay or long-term neurologic impairment.[2,3] Complications of PTB remain one of the leading causes of death globally in children younger than 5 years, accounting for more than one-third of deaths among neonates.[2,4] Spontaneous PTB (sPTB) represents a syndrome with multiple causes; however, one of the strongest risk factors of recurrence is a history of PTB, which increases the risk by 1.5- to 2-fold.[2] In addition, the number of previous PTBs and the gestational age of previous PTBs impact the recurrence risk.[2] Although the burden of PTB is clear, identifying strategies to reduce PTB has been challenging.

On October 29, 2019, a US Food and Drug Administration (FDA) advisory committee voted 9 to 7 to withdraw the approval of 17-alpha hydroxyprogesterone caproate (17OHP-C) for preventing recurrent PTB.[5] The original FDA approval was a result of the accelerated approval process for orphan drugs and

From the Department of Obstetrics and Gynecology, The University of Texas Southwestern Medical Center, Dallas, TX.

†Deceased.

Received Jan. 29, 2020; revised Sept. 18, 2020; accepted Sept. 21, 2020.

The authors report no conflict of interest.

Corresponding author: David B. Nelson, MD.
davidb.nelson@utsouthwestern.edu

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2020.09.045

Click Supplemental Materials under article title in Contents at ajog

Preterm birth is a substantial public health concern. In 2019, the US preterm birth rate was 10.23%, which is the fifth straight year of increase in this rate. Moreover, preterm birth accounts for approximately 1 in 6 infant deaths, and surviving children often suffer developmental delay or long-term neurologic impairment. Although the burden of preterm birth is clear, identifying strategies to reduce preterm birth has been challenging. On October 29, 2019, a US Food and Drug Administration advisory committee voted 9 vs 7 to withdraw interim accelerated approval of 17-alpha hydroxyprogesterone caproate for preventing recurrent preterm birth because the called for a confirmatory trial, known as the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial, was not confirmatory. The Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial included subjects enrolled in the United States and Canada to ensure that at least 10% of patients would be from North America; however, this trial took 9 years to complete and did not demonstrate significant treatment effects in the 2 primary outcomes of interest. Delivery before 35 weeks' gestation occurred in 122 of 1130 women (11%) given 17-alpha hydroxyprogesterone caproate compared with 66 of 578 women (11.5%) given placebo (relative risk, 0.95; 95% confidence interval, 0.71–1.26; P=.72). Similarly, the coprimary outcome neonatal composite index occurred in 61 of 1093 women (5.6%) given 17-alpha hydroxyprogesterone caproate compared with 28 of 559 women (5.0%) given placebo (relative risk, 1.12; 95% confidence interval, 0.68–1.61; P=.73). There was also a lack of efficacy for 17-alpha hydroxyprogesterone caproate treatment in the analysis of a variety of secondary outcomes. Like the Maternal-Fetal Medicine Units Network trial, the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery trial was also flawed. Importantly, the Maternal-Fetal Medicine Unit Network trial was the sole justification for treating women in the United States with 17-alpha hydroxyprogesterone caproate for nearly 2 decades. Currently, despite more than half a century, 17-alpha hydroxyprogesterone caproate still has not been found to be clearly effective. In this context, how does the advising physician dependent on scientific evidence advise a patient that 17-alpha hydroxyprogesterone caproate is effective when the evidence to support this advice has repeatedly been found to be inadequate? This clinical opinion is a critical appraisal of the 2 randomized trials examining the efficacy of 17-alpha hydroxyprogesterone caproate to prevent recurrent preterm birth and a chronicle of events in the regulatory process of drug approval to help answer this question. With this examination, these events illustrate the complexity of pharmaceutical regulations in the era of accelerated Food and Drug Administration approval and characterize the financial impact and influence in medicine. In this report, we also emphasize the value of observational studies in contemporary practice and identify other examples in medicine where accelerated Food and Drug Administration approval has been withdrawn. Importantly, the themes of the 17-alpha hydroxyprogesterone caproate story are not limited to obstetrics. It can also serve as a microcosm of issues within the US healthcare system, which ultimately contributes to the high cost of healthcare. In our opinion, the answer to the question is clear—the facts speak for themselves—and we believe 17-alpha hydroxyprogesterone caproate should not be endorsed for use to prevent recurrent preterm birth in the United States.

Key words: 17-alpha hydroxyprogesterone caproate, accelerated approval, evidence-based medicine, Food and Drug Administration, healthcare cost, pharmaceutical industry, pregnancy, preterm labor, progesterone, progestin, progestogen, randomized clinical trial, real-world evidence, regulatory process, subgroup analysis, withdrawal

Nelson et al. AJOG 2021

The 17-alpha hydroxyprogesterone chronicle

TO THE EDITORS: Nelson et al[1] have presented a thorough review of the status of 17-alpha hydroxyprogesterone caproate (17-P, 17-OHPC) and have reached the only appropriate conclusion. We had submitted a citizen petition to the Food and Drug Administration (FDA) in November 2020, outlining the same arguments and recommendation. Despite it being more than 2.5 years since the publication of these results and the FDA advisory committee's vote to withdraw approval, and more than 20 months since the FDA indicated its intent to withdraw approval, the FDA has yet to take final action. This situation cannot continue, for all the reasons cited by Nelson et al.[1]

Furthermore, the authors highlighted another troubling issue concerning corporate financial sponsorship in medicine. The Society for Maternal-Fetal Medicine (SMFM) published a "statement" in July 2020, endorsing the use of 17-OHPC.[2] In contrast to the disclosures required of authors of publications or presenters at meetings, the statement only indicated that the undisclosed committee members have filed a conflict of interest disclosure and that "all conflicts have been resolved through a process approved by the executive board." This was hardly a transparent process, particularly because of AMAG Pharmaceuticals' financial support of SMFM, and left the question of equipoise in evaluating the data open to question. This point has been made previously,[3] but it remains unaddressed. We should expect no less level of transparency from our professional organization than we require from individual authors, particularly as the former carries significantly more weight in medical and legal practices. ■

Jack Fitzsimmons, MD
Wadia Mulla, MD
Department of Obstetrics, Gynecology, and Reproductive Sciences
Lewis Katz School of Medicine
Temple University
3401 N. Broad St.
Philadelphia, PA 19140
Jmfitz1111@aol.com

The authors report no conflict of interest.

REFERENCES

1. Nelson DB, McIntire DD, Leveno KJ. A chronicle of the 17-alpha hydroxyprogesterone caproate story to prevent recurrent preterm birth. Am J Obstet Gynecol 2021;224:175–86.
2. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Statement: use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Am J Obstet Gynecol 2020;223:B16–8.
3. Rubin R. Confirmatory trial for drug to prevent preterm birth finds no benefit, so why is it still prescribed? JAMA 2020;323:1229–32.

 https://doi.org/10.1016/j.ajog.2022.03.033

Reply: The longest day soon comes to an end

We thank Drs Fitzsimmons and Mulla for their letter and interest in the chronicle of 17-alpha hydroxyprogesterone caproate (17-OHPC) for the prevention of recurrent preterm birth.[1] The time following the October 29, 2019, US Food and Drug Administration (FDA) advisory committee vote, to withdraw accelerated approval of 17-OHPC for the prevention of recurrent preterm birth, seems long ago—in a time predating the COVID-19 pandemic.[2] The month of March 2022 marks the 3 years since AMAG Pharmaceuticals announced the topline results of the Prevent Recurrent Preterm Birth in Singleton Gestations trial, and a public hearing has still not yet been posted.[3,4] In that time, we lost Dr Ken Leveno, senior author of our original report of 17-OHPC ineffectiveness and subsequent commentary, who passed away on May 2, 2020.[5]

It would seem that the story of 17-OHPC has stalled. However, at a closer look, the story continues to evolve. First, in a letter to Dr Patrizia Cavazzoni, acting director for the Center for Drug Evaluation and Research (CDER), dated October 14, 2020, AMAG Pharmaceuticals requested an extension to the public hearing.[6] Second, in the same month, the Covis Group and AMAG Pharmaceuticals announced that they had entered into a definitive agreement under which the Covis Group would acquire AMAG Pharmaceuticals for $13.75 per share in cash, or approximately $498 million on a fully diluted basis and approximately $647 million on an enterprise basis, including debt obligations expected to be assumed or repaid net of cash.[7] Once more, the financial scope of the pharmaceutical industry is staggering as we noted in our previous report.[1]

Since October 2020, the US FDA CDER and the Covis Group have been volleying challenges and rebuttals to the content, scope, and structure of the requested public hearing. A nested story within the story of 17-OHPC can be found in the catalog of documents for the "Proposal to withdraw marketing approval; notice of opportunity for a hearing" at the regulations.gov website.[8] At the time of this writing, more than 140 documents have been uploaded, including statements from national organizations, members of the US Congress, and physicians arguing for and against the withdrawal of 17-OHPC

Nelson et al. AJOG 2022

1. CDER dated 14 Oct 2020, **AMAG Pharmaceuticals requested extension** to public hearing.
2. Covis Group acquire AMAG Pharmaceuticals for $13.75 per share in cash ($498M) on a fully diluted basis and approximately **$647M** on enterprise basis
3. Since Oct 2020, **Covis** Group and **CDER** volleying challenges and rebuttals to content, scope, and structure of the requested public hearing.

UTSouthwestern Medical Center

In 2022…October 17-19, 2022

ADVISORY COMMITTEE MEETING

UPDATED INFORMATION: October 17 – 19, 2022: Hearing Announcement involving the Obstetrics, Reproductive, and Urologic Drugs Advisory Committee

OCTOBER 17 - 19, 2022

Share | Tweet | Linkedin | Email | Print

On This Page

- Meeting Information
- Event Materials

Date: October 17 - 19, 2022
Day1: Mon, Oct 17 8:00 AM - 4:00 PM ET
Day2: Tue, Oct 18 8:20 AM - 4:00 PM ET
Day3: Wed, Oct 19 8:30 AM - 12:15 PM ET

1. Do the findings from Trial 003 verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

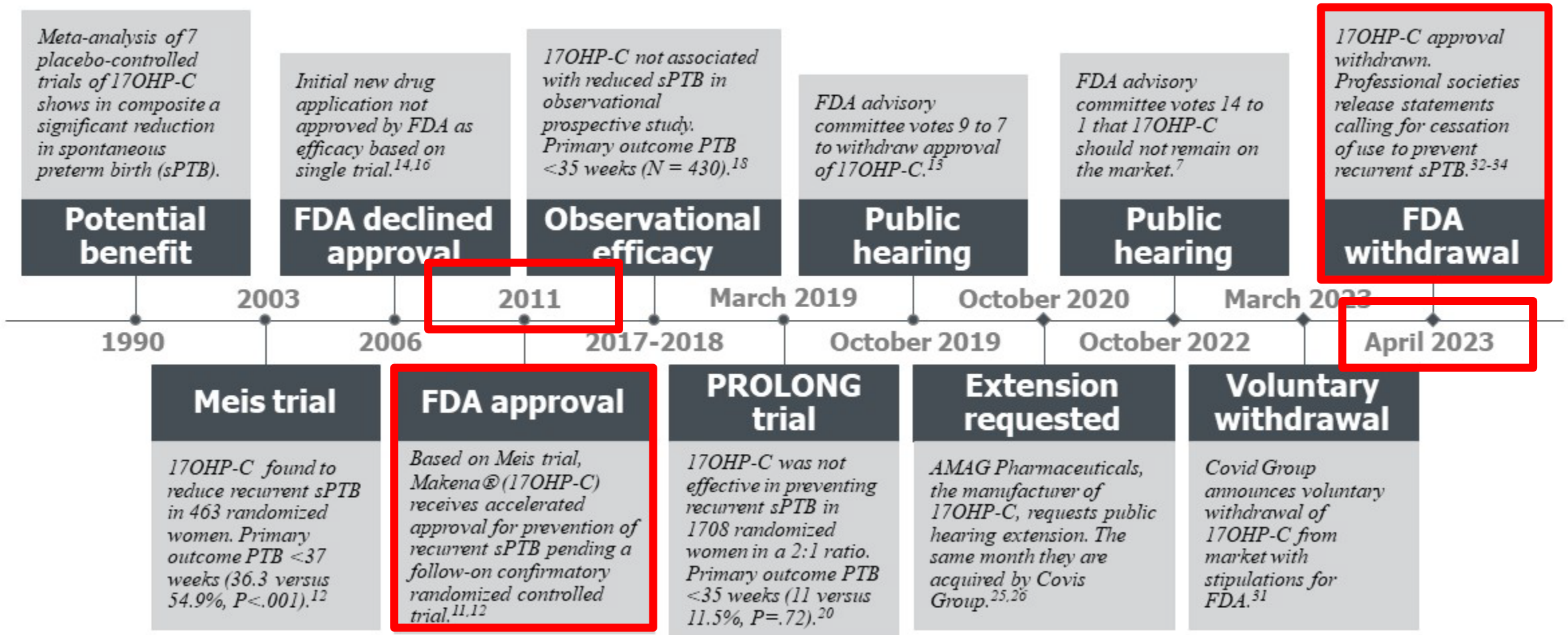
2. Does the available evidence demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth?

3. ***Should FDA allow Makena to remain on the market?***

As part of that discussion, you may discuss:
whether the benefit-risk profile supports retaining the product on the market;
what types of studies could provide confirmatory evidence to verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth?

FDA. 2022

Timeline of US FDA Accelerated Approval and Withdrawal of 17OHP-C



Nelson DB et al. Am J Obstet Gynecol. 2023

In 2023…National Organization Responses

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Statement

smfm.org

Check for updates

Society for Maternal-Fetal Medicine Statement: Response to the Food and Drug Administration's withdrawal of 17-alpha hydroxyprogesterone caproate

Society for Maternal-Fetal Medicine (SMFM); SMFM Publications Committee

On April 5, 2023, the US Food and Drug Administration withdrew the approval of 17-alpha hydroxyprogesterone caproate, effective immediately, because of the lack of evidence that it reduces the risk of recurrent spontaneous preterm birth. This decision withdraws approval for all formulations of 17-alpha hydroxyprogesterone caproate (both intramuscular and subcutaneous) and applies to both brand name (Makena) and generic versions of the medication. We agree with the Food and Drug Administration determination and discourage continued prescribing of 17-alpha hydroxyprogesterone caproate, including through compounding pharmacies. We do not recommend changing indications for cerclage, indications for vaginal progesterone in patients with a short cervix, or recommendations against activity restriction based on the Food and Drug Administration withdrawal of 17-alpha hydroxyprogesterone caproate from the market. We recommend that discussion of the use of vaginal progesterone for primary prevention of recurrent preterm birth without input of cervical length or in those with a cervical length of ≥25 mm includes a shared decision-making process, especially if a progesterone formulation for preterm birth prevention was received in a previous pregnancy. The Food and Drug Administration determined that it would be inappropriate to delay the effective date of the withdrawal to allow patients currently receiving 17-alpha hydroxyprogesterone caproate to finish treatment. We agree with the Food and Drug Administration that there is no evidence of benefit with continued treatment. Patients currently receiving 17-alpha hydroxyprogesterone caproate can be counseled that the Food and Drug Administration's Center for Drug Evaluation and Research has not identified evidence of harm from discontinuation before 37 weeks of gestation.

Key words: 17-alpha hydroxyprogesterone caproate, cerclage, Food and Drug Administration, preterm birth, vaginal progesterone

Introduction

In 2011, the US Food and Drug Administration (FDA) approved intramuscular 17-alpha hydroxyprogesterone caproate (17-OHPC; marketed as Makena) for the sole indication of reduction of recurrent spontaneous preterm birth (PTB) in pregnant people with a singleton pregnancy who had a previous singleton spontaneous PTB. Under typical FDA drug approval processes, at least 2 appropriately designed clinical trials must demonstrate efficacy for a medication to receive approval. Because of the public health burden of PTB and the lack of other effective interventions at the time, the FDA granted 17-OHPC accelerated approval,[1] largely based on the positive findings of the Maternal-Fetal Medicine Units (MFMU) Network study conducted by Meis et al,[2] with the requirement that a second confirmatory study be conducted.

Corresponding author: Society for Maternal-Fetal Medicine (SMFM) Publications Committee. pubs@smfm.org

The Progestin's Role in Optimizing Neonatal Gestation (PROLONG) study, a multicenter, multinational study conducted largely outside of the United States, was conducted from 2009 to 2018 to meet this requirement.[3] The study had 2 coprimary outcomes: PTB at <35 weeks of gestation and composite neonatal morbidity and mortality. Except for the primary outcomes and recruitment locations, study investigators designed the PROLONG study to mimic the original MFMU study protocol as much as possible.[4] Despite this, the PROLONG study failed to demonstrate either reduction in spontaneous PTB or improvement in neonatal outcomes among participants treated with 17-OHPC compared with participants treated with placebo.

Food and Drug Administration review since the publication of Progestin's Role in Optimizing Neonatal Gestation

After the publication of the PROLONG study in 2020, the FDA's Center for Drug Evaluation and Research (CDER)

SMFM. 2023

News Releases | Apr 7, 2023

Share | Print

ACOG Statement on the FDA Withdrawal of 17-OHPC

Washington, D.C. *— Christopher M. Zahn, MD, FACOG, chief of Clinical Practice and Health Equity and Quality, for the American College of Obstetricians and Gynecologists (ACOG), issued the following statement:*

"After a years-long process to determine the efficacy of the only previously approved treatment option to prevent recurrent, spontaneous preterm birth, the U.S. Food and Drug Administration (FDA) made a final decision Thursday to withdraw approval of Makena (17-OHPC) and its generics.

"We have understood for some time that this was a possible outcome. The unfortunate result is that patients now have no FDA-approved treatment option available to them and obstetricians-gynecologists are left with limited options to prevent a condition that affects roughly 10 percent of U.S. births and is the leading cause of neonatal morality.

"To assist obstetrician-gynecologists in their decision-making regarding the administration and prescribing of the remaining supply of 17-OHPC and other immediate concerns regarding generics and compounding, ACOG has issued a set of Frequently Asked Questions.

ACOG. 2023

Are we at the end of road? (To summarize…)

- Burden of preterm birth is serious.
- Poorly understood pathophysiology…and mechanisms of action for prevention therapies.
- Complex history of progestogens to prevent recurrent preterm birth in singleton pregnancies.
- Tremendous healthcare costs associated with medication use.

Table. Utilization, Cost, and Outcome Comparison Between Branded and Compounded 17-Alpha Hydroxyprogesterone Caproate, 2008-2015

Variable	Branded Drug	Compounded Drug
Total women users, No.	535	3350
Total pregnancies, No.	540	3481
Length of treatment, mean (SD), wk	17.7 (5.1)	17.3 (5.4)
Preterm deliveries (rate), No. (%)	129 (23.9)	878 (25.2)
Drug cost per pregnancy, mean (SD), $US	10 917 (4248)	206 (115)
Users with an infection (sepsis or bacterial meningitis), No.	1	1
Maternal age, mean (SD), y	33.0 (4.9)	32.7 (4.9)
Stillbirths (rate), No. (%)	5 (0.93)	36 (1.03)
Total amount spent, $US	5 895 060	718 266

Fried I, et al. JAMA Intern Med 2017;177:1689-90.

Accelerated Approval Challenged

VIEWPOINT

The FDA Struggle to Withdraw Makena
Problems With the Accelerated Approval Process

Daniel G. Aaron, MD, JD
Harvard Law School, Cambridge, Massachusetts; and US Court of Appeals for the Sixth Circuit, Louisville, Kentucky.

I. Glenn Cohen, JD
Harvard Law School, Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics, Harvard University, Cambridge, Massachusetts.

Eli Y. Adashi, MD, MS
Department of Medical Science, Brown University, Providence, Rhode Island.

Viewpoint page 2392

Hydroxyprogesterone caproate (Makena) is an injectable drug for the prevention of preterm birth, ie, birth prior to 37 weeks of gestation. About 1 in 10 US infants is born preterm,[1] a condition that is increasing in the US and is responsible for about 75% of perinatal mortality and about half of neonatal morbidity.[1,2] The US Food and Drug Administration (FDA) approved Makena through its accelerated approval pathway in 2011. In this Viewpoint, we discuss the controversy surrounding the current efforts of the FDA to withdraw Makena from the market and the implications for the broader accelerated approval pathway.

Although clinical trials usually measure clinical end points, the FDA accelerated approval program, launched in 1992, speeds drug development by liberalizing the use of surrogate end points for serious or life-threatening conditions. In considering the use of surrogate end points in this pathway, the FDA is permitted to take into account the need for treatments and the severity and prevalence of a disease. However, applicants must conduct phase 4 confirmatory trials to verify clinical benefit, and poor results can lead to the withdrawal of the drug.

> The delay in withdrawing Makena has proven costly for the Centers for Medicare & Medicaid Services...and for the patients who are exposed to adverse effects with little or no clinical benefit.

It was 1975 when a small clinical trial concluded that the gestational administration of hydroxyprogesterone caproate lengthened pregnancy and reduced neonatal mortality.[3] In the wake of additional research in this arena, then-manufacturer Adeva applied to the FDA for approval of hydroxyprogesterone caproate for reducing the risk of preterm birth in women with a history of preterm birth. The FDA granted the accelerated approval in 2011. Not everyone at the agency supported the decision. An FDA report identified several statistical problems in the single study supporting approval and concluded that "the information and data...do not provide convincing evidence" of effectiveness.[4] The report further suggested delaying approval until interim results became available from yet another clinical trial. However, in its risk-benefit calculus, the FDA indicated that it was convinced by the public health importance of preterm birth and the lack of existing treatment.[5] Although the FDA granted accelerated approval, it required the company to proceed with a confirmatory trial, which had begun enrollment and was to be completed in 2016.

The confirmatory trial results became available in 2019, 3 years after the trial's projected completion date. The data proved disappointing, thereby leading an advisory committee in 2019 to conclude unanimously that the new trial did not confirm clinical benefit. Three years later, the FDA is still attempting to remove Makena from the market. Although the FDA has concluded that Makena lacks substantial evidence of effectiveness, the manufacturer refused to withdraw the drug voluntarily and requested a hearing. The FDA asserted in briefing documents that continued marketing of Makena "would undermine the integrity of the accelerated approval pathway."[6] After a 3-day hearing in October 2022, an FDA advisory panel voted 14-1 that Makena should be withdrawn. The current manufacturer of the drug, Covis Pharma, is vigorously contesting FDA action.[7]

The Makena story raises questions about the accelerated approval pathway's implicit promise: approval can be provided on an expedited basis with the ability to quickly withdraw drugs that fail confirmatory trials. In this case, the delay in effectuating withdrawal has been dramatic. Although some of the delay is no doubt attributable to the emergence of COVID-19 in 2020 and its sapping of FDA resources, other elements were also at play. For the FDA to withdraw a drug, the statute and regulations require an informal hearing, which includes the convening of an advisory committee and the preparation of extensive materials for the hearing. The Makena docket has 241 documents and the hearing lasted 3 days. The FDA is expending considerable resources to build the record for withdrawal, given the possibility that the aggrieved company will ultimately take it to court. The FDA has only once before exercised its authority to withdraw an accelerated approval indication against a company's wishes, in the case of bevacizumab (Avastin), which had been approved for use in the treatment of breast cancer. A recent bill[8] would have attempted to facilitate withdrawals of accelerated approval by removing the informal hearing requirement.[7] However, the proposed substitute procedure was also quite cumbersome—including notice-and-comment procedures for each withdrawal and convening of an advisory committee upon industry's request. In any event, although the bill in question passed the House of Representatives, it "died" in the Senate.[7]

Attempts to withdraw a drug like Makena also put the FDA in a difficult position. Despite poor confirmatory trial

Corresponding Author: Daniel G. Aaron, MD, JD, Heyman Fellow at Harvard Law School (daaron@jd20.law.harvard.edu).

JAMA December 27, 2022 Volume 328, Number 24 jama.com

Aaron DG et al JAMA. 27 Dec 2022

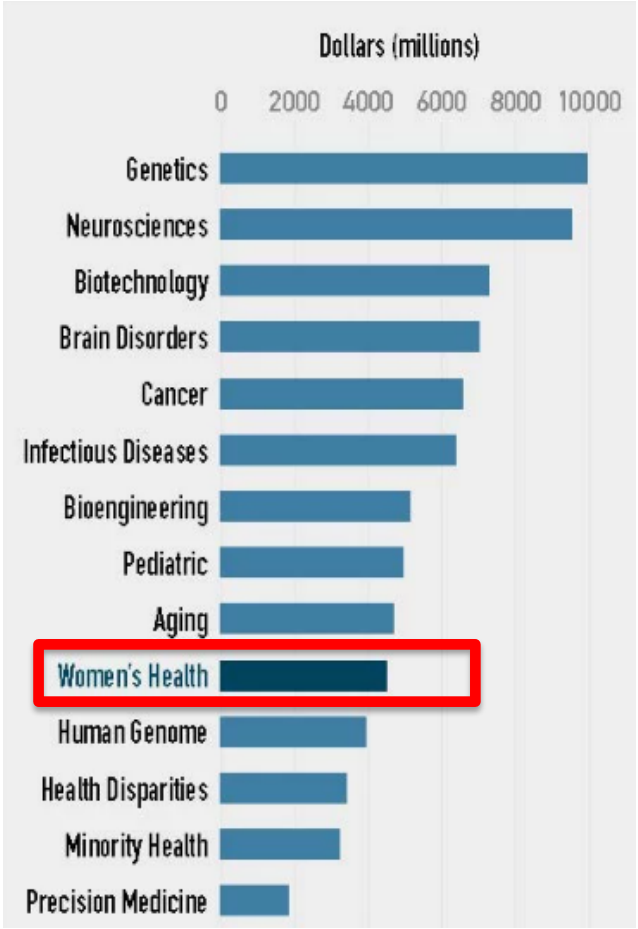
What might be done? Given all the difficulties associated with the withdrawal of a drug that has gone through accelerated approval, one solution would be to require a stronger signal of efficacy before that approval is ever granted. One might worry that the more evidence the FDA requires upfront, the more the accelerated approval will devolve into a traditional approval process. This is a misunderstanding of the pathway. Accelerated approval was never meant to permit a reduction in the evidentiary standard for new drugs. Rather, it was intended to allow a more liberal use of surrogate end points. Hueing closer to the pathway's original intent may yield more dependable drugs for the US population. Congress may wish to place more guardrails on the evidence required before a drug comes to market under this pathway, for example, by reaffirming a strict requirement for 2 supportive clinical trials—only 1 was available for Makena. Some might argue that it is wiser to allow a lower evidentiary standard when there is a serious unmet health need, but the Makena case study illustrates the serious risk in permitting the sale of drugs with weak evidence of effectiveness. A different approach, as suggested by a proposed bill,[10] is for accelerated approval to automatically expire after a defined period of time unless the FDA confirms that the approval is warranted. This would make withdrawals automatic if a sponsor fails to provide sufficient evidence to persuade the agency.

The end is where we start from…

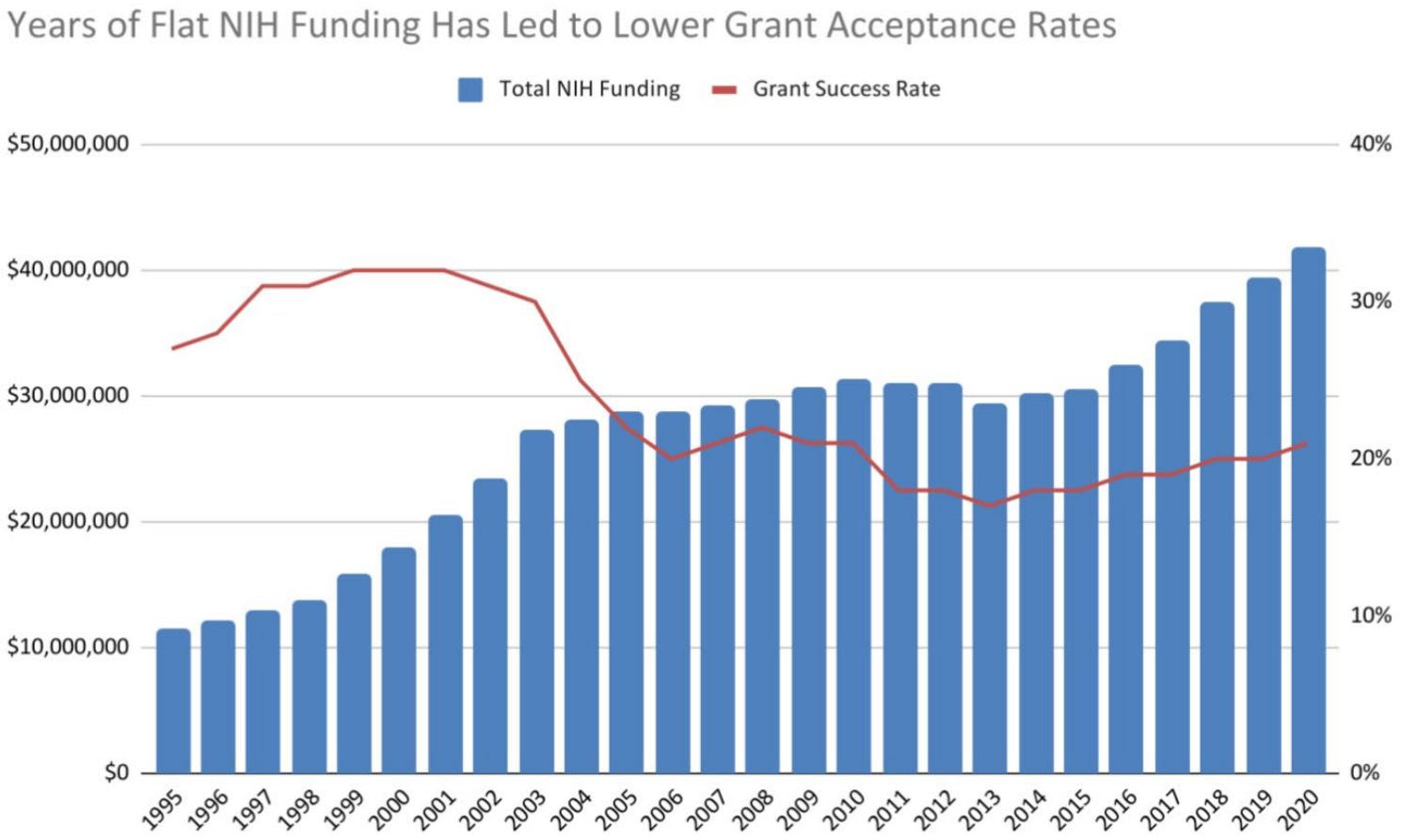
- Human data on pregnancy and lactation are available in **<20% of new product labeling** following the FDA Pregnancy and Lactation Labeling Rule.
- Caution against the "creep" of **interventions in the absence of data**.
- Some may continue to explore 17OHP-C. **Understanding the pharmacologic properties** of medications should be a first step rather than an afterthought.
- As long as we keep treating spontaneous preterm birth as a single entity and continue to try to address it with a single intervention, we will likely continue to fail—**understanding the mechanism of the disease we are treating**.
- Beginning with the original report on 17OHP-C, and carried forward today, obstetrical providers are encouraged to **measure what we do and report what we find**—either positive or negative—to share experiences.

Nelson DB et al. Am J Obstet Gynecol. 2023

Selected categories of NIH Research Funding From Research, Condition & Disease Categories



Spong CY. Addressing inequalities in women's health research. Contemporary OB/GYN Journal. 2020



Rubin K. Why scientists struggle to get funding for women's health. 2022.

Concluding remarks from US FDA Advisory Committee, October 19, 2022

*"The compulsion to do something is strong…there needs to be another trial because I want to believe that there is a solution for preterm birth…**But I think that when we leave something on the market that hasn't been shown to be effective, we lose out on other investigations that might be pursued. We spend money that could be spent elsewhere for all of the many problems in maternal and child health that need our attention. And the last thing I would say is that, again, faced with that powerless feeling, is false hope really any hope at all?***

So I hope that in the future, we are able to do a study that shows us who the population is that will benefit from this medication, if any, and when we have that evidence, we're able to go to that patient population confidently and say this is the thing that I think will help you."

–Dr. Anjali Kaimal

Thank you

Obstetrics and Gynecology

Leadership | Faculty | Education & Training | History | Research | Patient Care | Contact Us | Divisions

- Founding of the Department
- Overview of Laboratory Research
- Emeritus Chairs
- Professors Emeritus
- In Memoriam
  - Gary Ackerman, M.D.
  - **Kenneth J. Leveno, M.D.**

Kenneth Leveno, M.D. – 1941-2020

He transformed the way obstetrical care was delivered and simultaneously touched the lives of patients and the obstetricians he mentored.

With the passing of Kenneth J. Leveno, M.D., on May 2, 2020, we lost one of the most influential and transformative leaders in obstetrics. The architect of what became known as "Parkland obstetrics," he was passionate that quality care be delivered to all, without regard for socio-economic status.

During his 42-year career at UT Southwestern and Parkland Memorial Hospital, Dr. Leveno was responsible for a number of innovations that reduced congestion, relieved overburdened house staff, and improved patient access to care. To facilitate the latter, he built an obstetrical service that integrated prenatal, delivery, and postpartum care into a unified system. He developed a low-risk delivery unit and created a nurse midwifery service. As a result of these innovations, 97% of women delivering at Parkland have received prenatal care.

Those achievements alone would be sufficient for one lifetime. But Dr. Leveno had more to offer. An editor of the seminal textbook, *Williams Obstetrics*, Dr. Leveno co-authored the 19th through 25th editions. He was a physician–scientist, leader, and a mentor with a mission that was inspirational and a focus that was laser sharp. Under his leadership, the way obstetricians were trained changed, and medical students who never dreamed of a career in obstetrics became "converts."

Why sign up for one of the busiest maternity services in the nation? The answer was at once simple and complex. Dr. Leveno never lost sight of the patient. He set a high bar for himself and for those he taught. He constantly reminded physicians that *they* were responsible for measuring and improving the quality of care they provided. He taught them to write and challenged them "to think critically and to think big." Even when the burdens of the service became onerous and deliveries topped 16,000 annually, he reminded residents and fellows that each of those 16,000 women was an individual who entrusted her life to their care, and it was *their* responsibility to treat her with dignity and provide the best care possible.

Kenneth Leveno, M.D.

- **Medical School:** Creighton University School of Medicine
- **Internship:** Creighton University School of Medicine, General Surgery
- **Residency:** St. Joseph's Hospital, Phoenix, AZ, Obstetrics and Gynecology
- **Fellowship:** University of Texas Southwestern Medical Center, Maternal–Fetal Medicine
- **Subspecialty:** Maternal–Fetal Medicine
- **Years of Service:** July 1, 1978 – May 2, 2020

Congressional Tribute