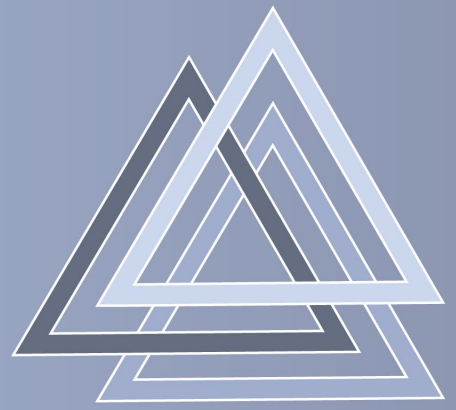


# SAAOG

## Annual Meeting • 2024

January 20-23 • The Cloister at Sea Island

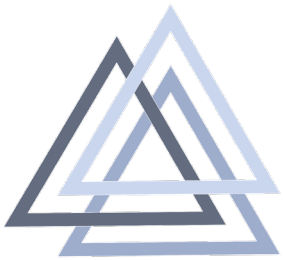
# PROGESTERONE AND PARTURITION

Haywood L. Brown, MD

Professor Obstetrics and Gynecology

Morsani College of Medicine

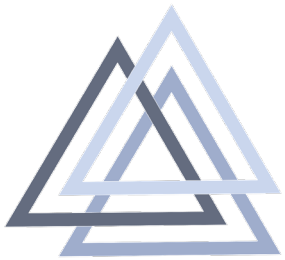
University South Florida



# Learning Objective

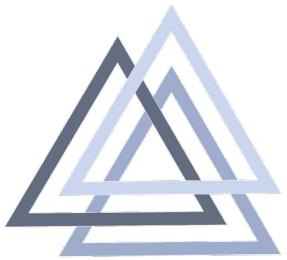
At the Conclusion of this Presentation the Participants will be Able to:

1. Discuss the epidemiology of preterm birth, racial disparity and challenges of  prevention of prematurity
2. Discuss the historical role of progesterone in normal and early parturition.
3. Discuss the current recommendations for the use of progesterone in prematurity prevention guided by current evidence.



# Disclosures

- Hologic - Consultant
- Myriad - Consultant
- HRSA AIM Community Care Initiative – Co PI
- Assess to Carrier Screening Coalition – Medical Advisor



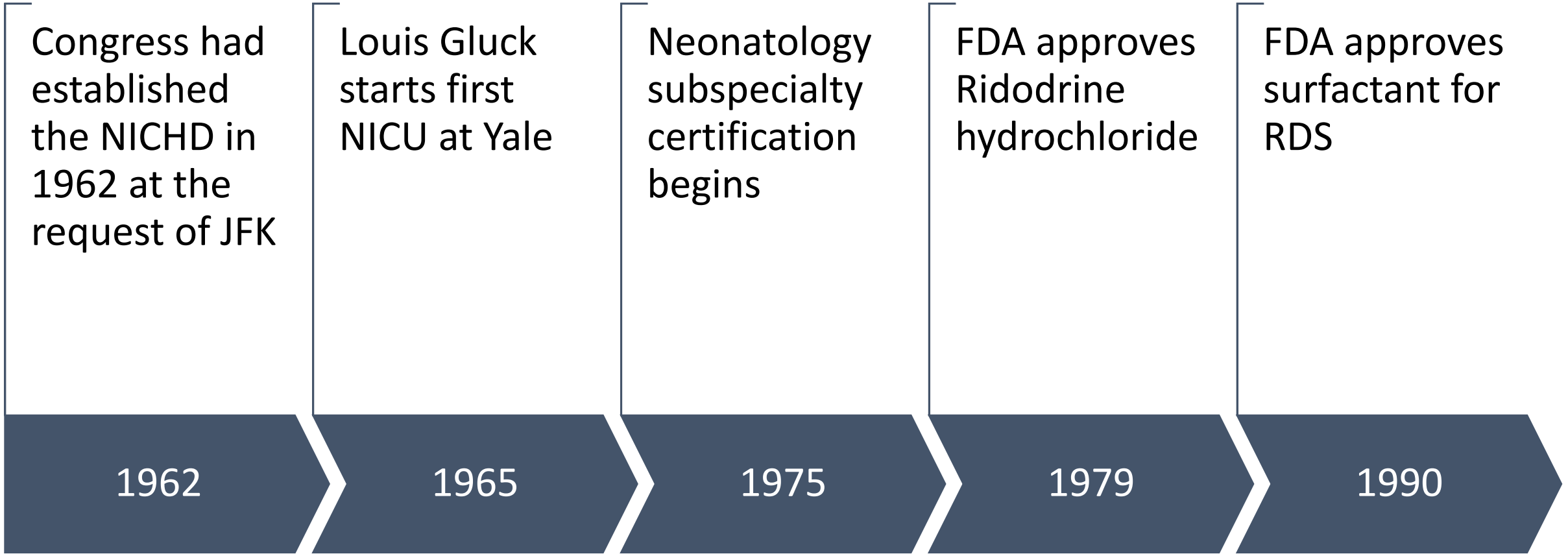
# HISTORY OF MANAGEMENT OF PRETERM BIRTH – RECOGNITION OF THE PROBLEM

- Patrick Bouvier Kennedy (Aug 7, 1963 – Aug. 9, 1963)
- 5 and a half weeks early; 2100 gms (4 lbs, 10 oz.)
- According to *The New York Times,* the treatment for hyaline membrane disease was “to monitor the infant’s blood chemistry…”
- Sparked public awareness of the disorder

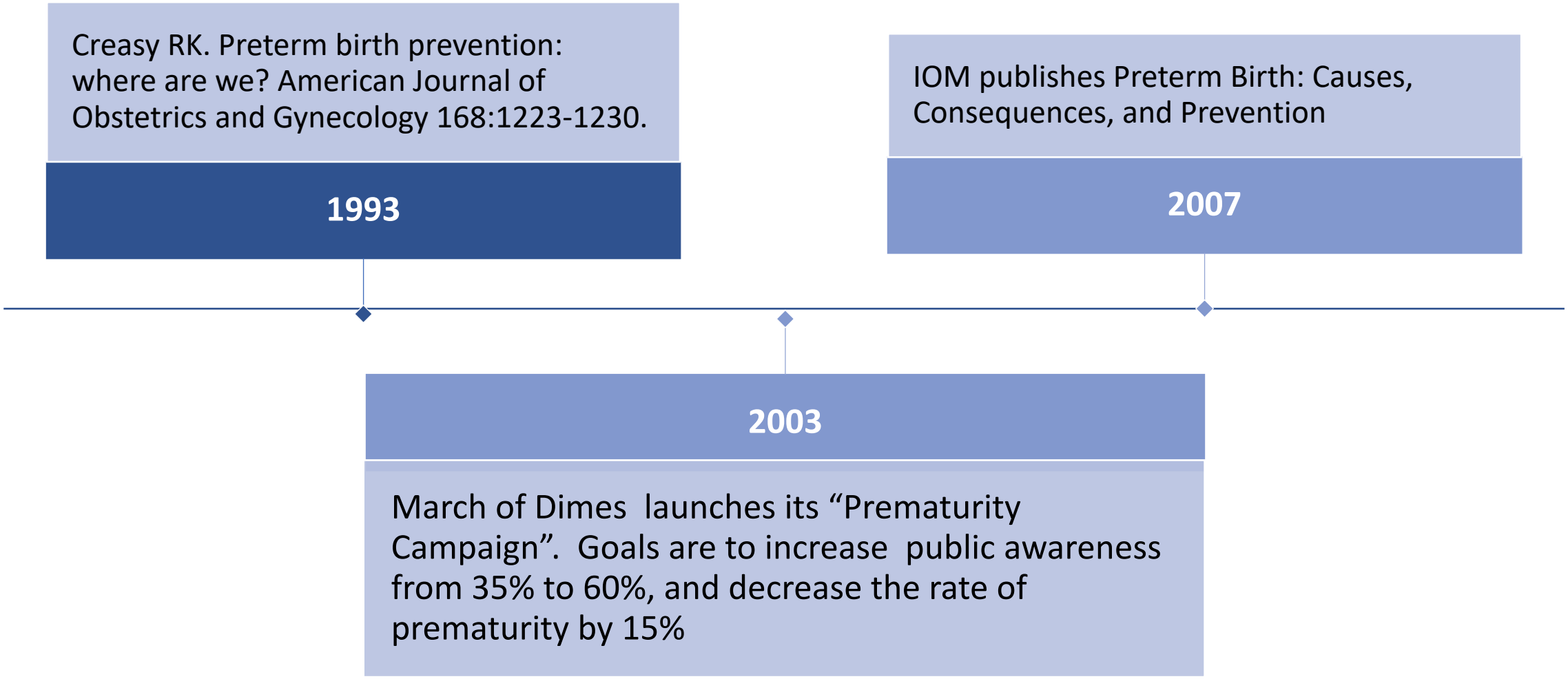
# HISTORY OF MANAGEMENT OF PRETERM BIRTH – THE FIRST THREE DECADES (1960’’s-1990’S)

- Identification and recognition of scope of the problem
- Treatments for preterm labor
- Efforts to identify pathophysiology
- Risk scoring systems developed
- Recognition of the multi-factorial nature of preterm birth

# HISTORY OF MANAGEMENT OF PRETERM BIRTH – RESPONSE TO THE PROBLEM



# EFFORTS PRETERM BIRTH PREVENTION



# PRETERM BIRTH WORLDWIDE

- An estimated 13. 4 million babies were born preterm in 2020 (before 37 completed weeks gestation)
- 152 million babies born before 37 weeks between 2010 and 2020
- Global preterm birth rate was 9.9% in 2020 compared with 9.8% in 2010.
- Preterm birth complications are the leading cause of death among children under 5 years of age; 1 million annually
- Three quarters of these deaths could be prevented with current, cost-effective interventions.

# PRETERM BIRTH WORLDWIDE

- Three quarters of these deaths could be prevented with current, cost-effective interventions.
- Across countries, the rate of preterm birth ranges from 4-16% of babies born in 2020
- Extreme preterm birth is significantly associated with long term disability specifically neurological

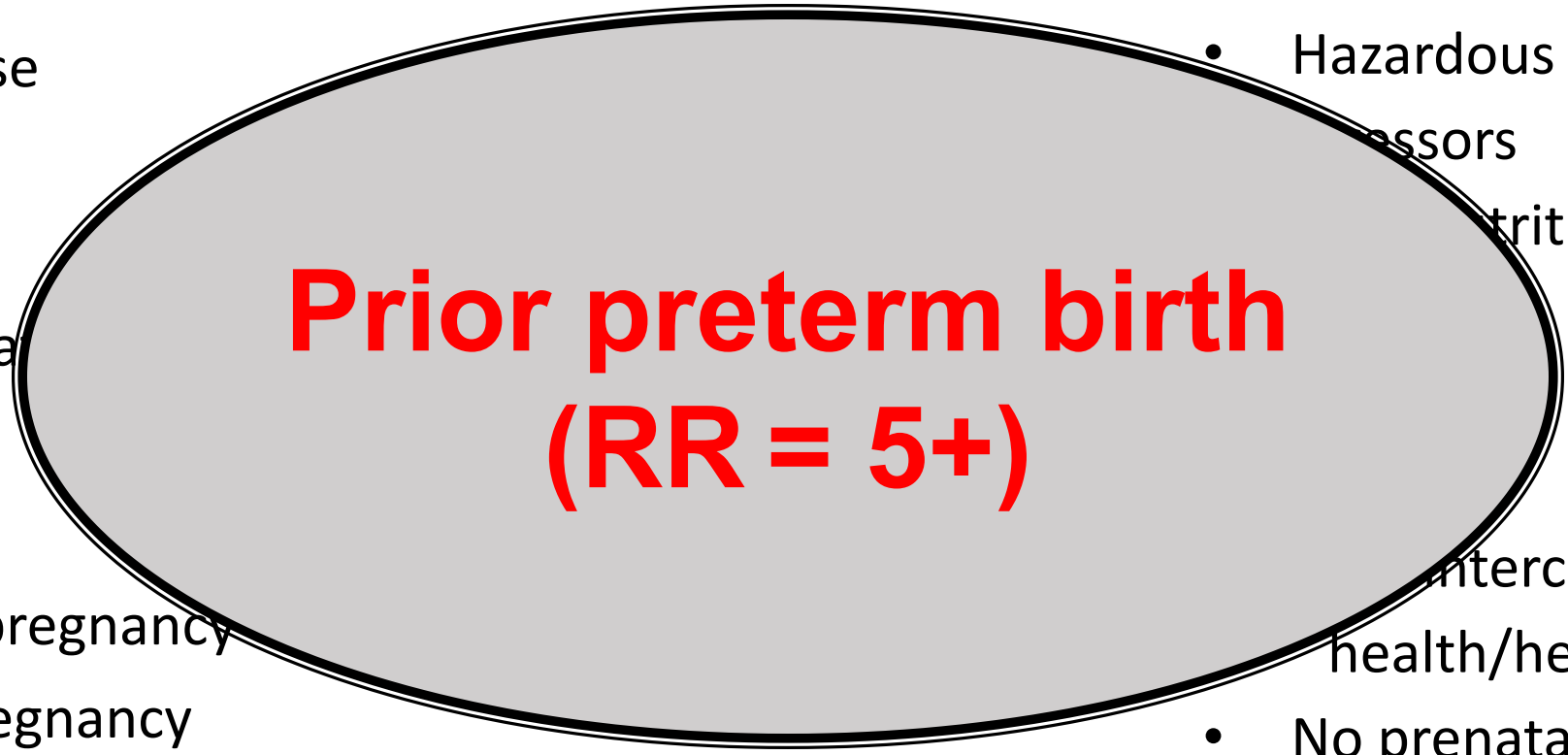
# RISK FACTORS FOR PRETERM BIRTH

Biology/Genetics

- Chronic disease
- Inflammation
- Infection
- Multiple gesta

Behavior

- Unintended pregnancy
- Short interpregnancy interval
- Alcohol/tobacco/drug use



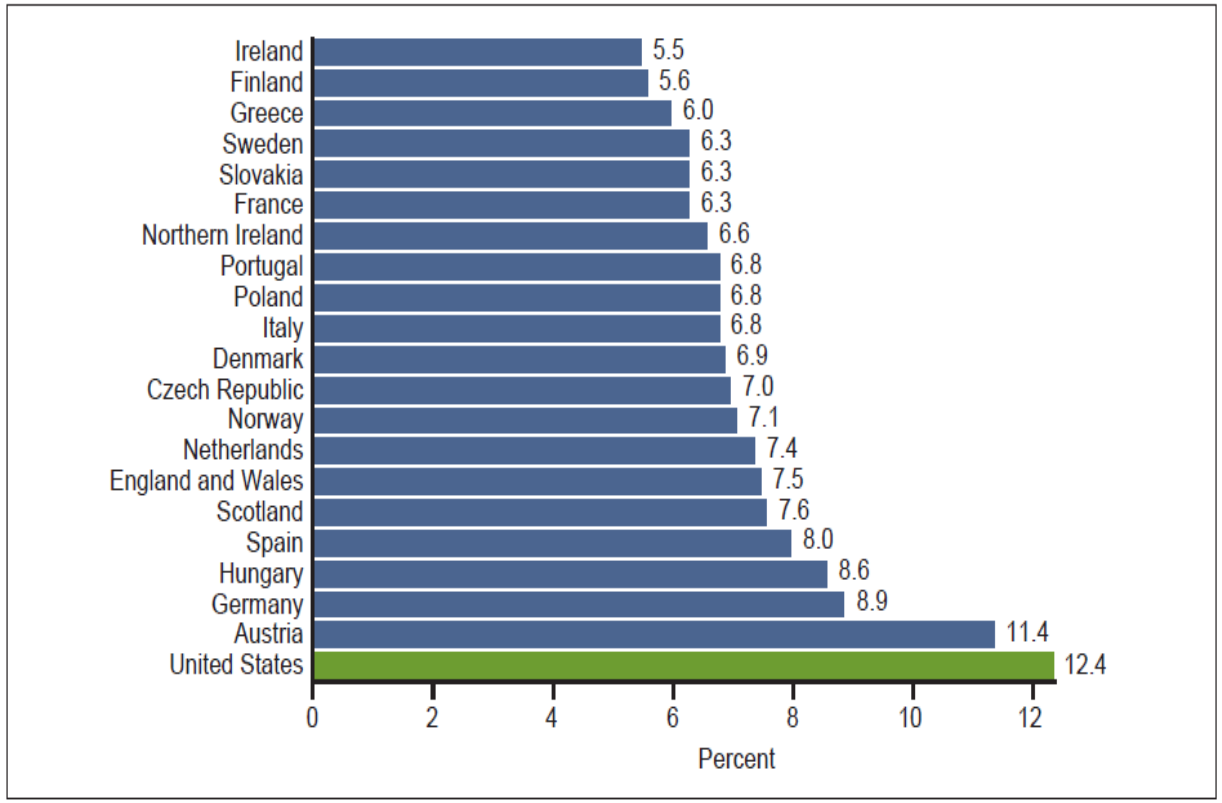

Environment

- Hazardous exposures
- essors
- trition

- nterconception health/health care
- No prenatal care

## The percentage of births that were born preterm was much higher in the United States than in Europe.

Figure 3. Percentage of preterm births, United States and selected European countries, 2004

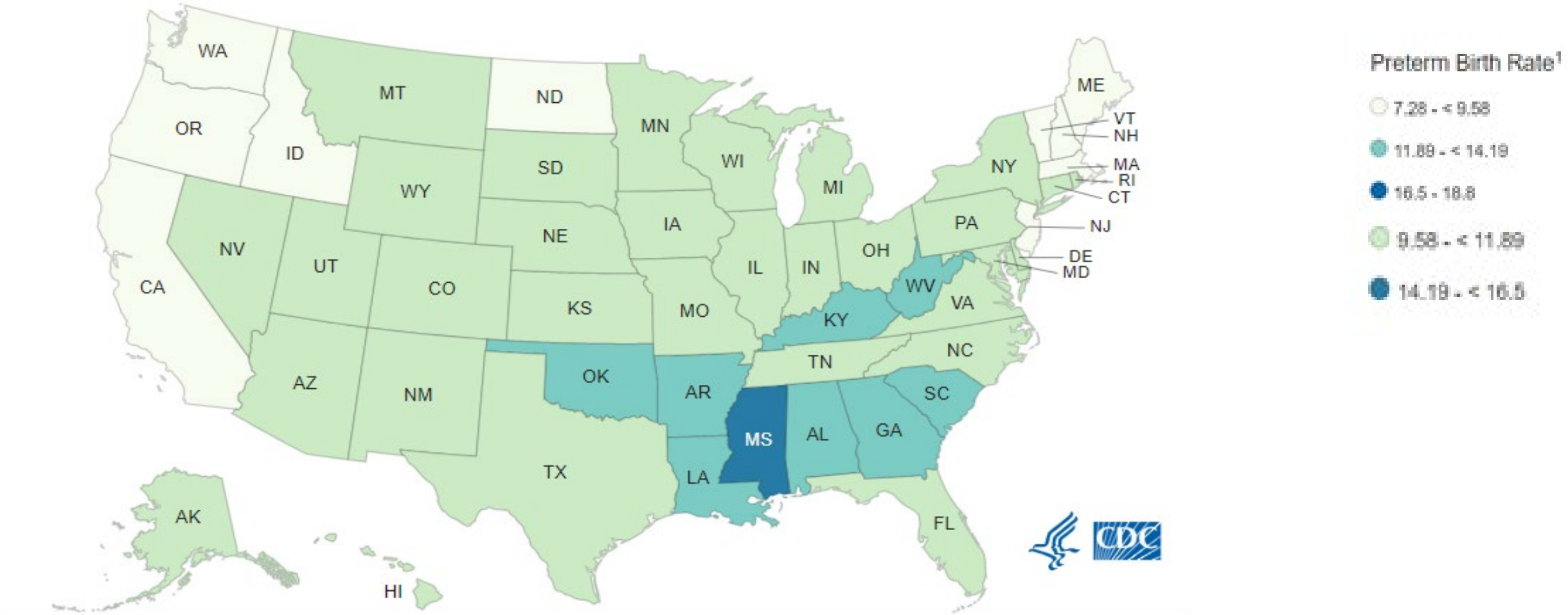



NOTE: Excludes births at less than 22 weeks of gestation to promote comparability between countries. Preterm births are those from 22 to 36 weeks of gestation.
SOURCE: NCHS linked birth/infant death data set (for U.S. data) and *European Perinatal Health Report* (for European data).

NCHS Data Brief, 2009

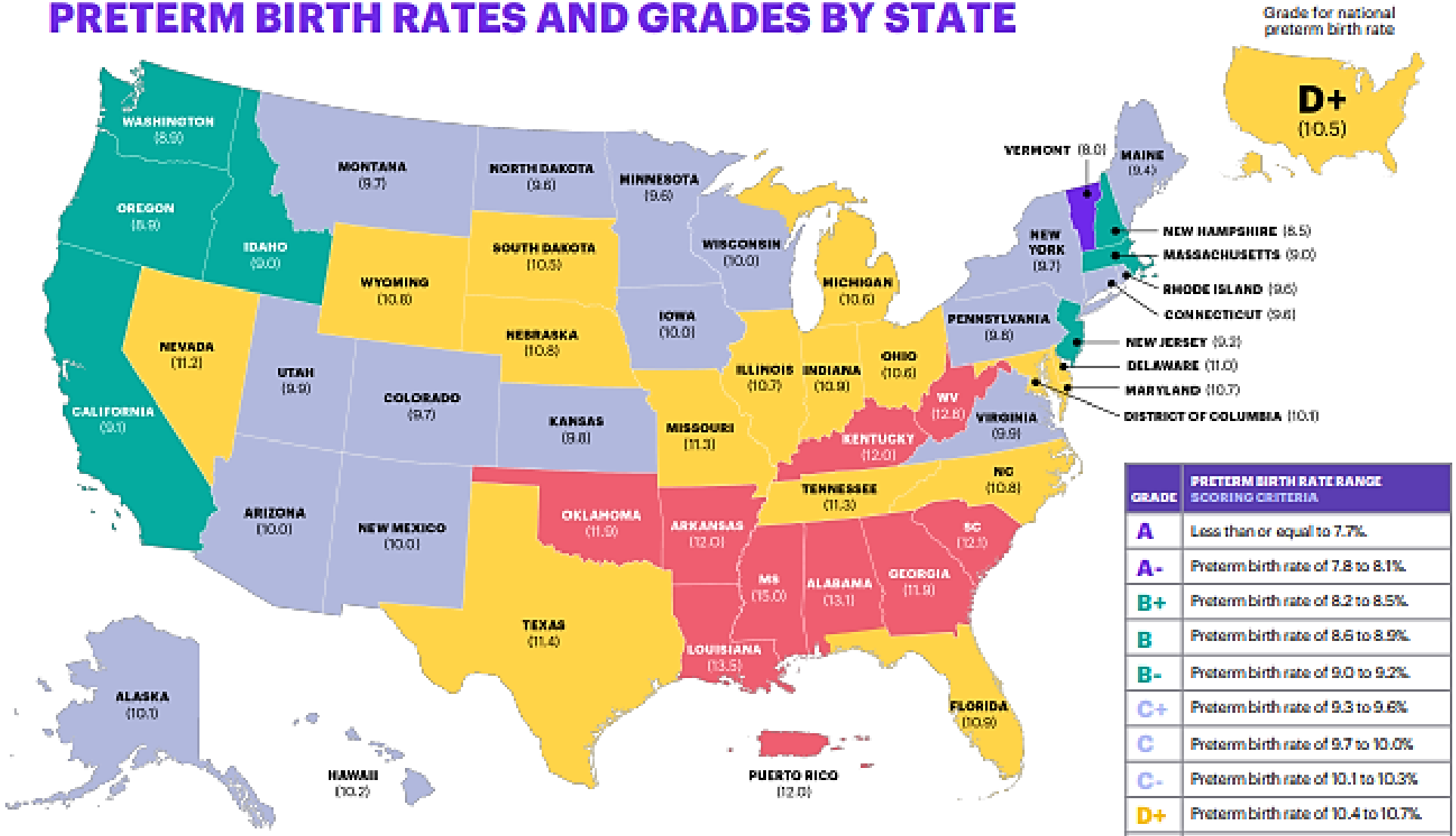
Rates of preterm birth range from 4 percent in Belarus to 18 percent in Malawi, and generally track poverty rates, the repo found. Nine of the 11 countries with preterm rates above 15 percent are located in sub-Saharan Africa. Comoros and Con have a rate of 16.7 preterm births per 100 live births; Zimbabwe, 16.6. The U.S. rate is 12 percent, the worst of the G8 countries and 59th of the 65 countries with reliable historical data.

# PRETERM BIRTH BY STATE 2021




Preterm Birth Rate[1]

# PRETERM BIRTH RATES AND GRADES BY STATE




| GRADE | PRETERM BIRTH RATE RANGE SCORING CRITERIA |
|---|---|
| A | Less than or equal to 7.7%. |
| A- | Preterm birth rate of 7.8 to 8.1%. |
| B+ | Preterm birth rate of 8.2 to 8.5%. |
| B | Preterm birth rate of 8.6 to 8.9%. |
| B- | Preterm birth rate of 9.0 to 9.2%. |
| C+ | Preterm birth rate of 9.3 to 9.6% |
| C | Preterm birth rate of 9.7 to 10.0% |
| C- | Preterm birth rate of 10.1 to 10.3% |
| D+ | Preterm birth rate of 10.4 to 10.7%. |
| D | Preterm birth rate of 10.8 to 11.1%. |
| D- | Preterm birth rate of 11.2 to 11.4%. |
| F | Preterm birth rate greater than or equal to 11.5%. |

Preterm is less than 37 completed weeks of gestation, based on obstetric estimate of gestational age.

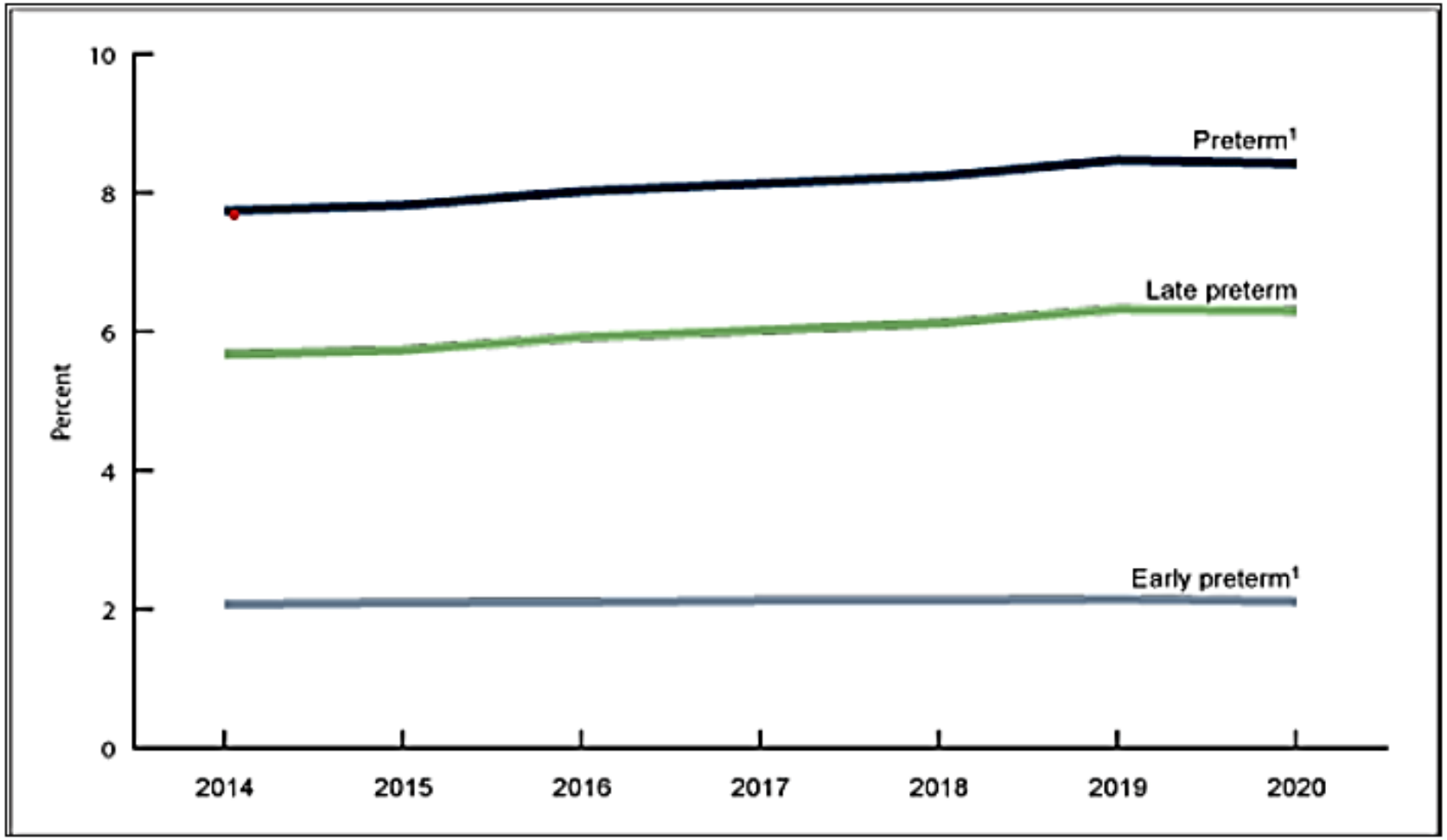
Grades assigned by March of Dimes Perinatal Data Center.

Puerto Rico is not included in the United States total.

**Source:** Preterm birth rates are from the National Center for Health Statistics, 2021 final natality data and U.S. Territories natality data.

# PREVENTION PRETERM BIRTH

Figure 1. Singleton preterm birth rates: United States, 2014–2020




[1]Significant decline between 2019 and 2020 ($p < 0.05$).

# RACIAL DISPARITY IN PRETERM BIRTH

Non-Hispanic Black women have a 2-fold greater risk for preterm birth compared with non-Hispanic white race. (95% CI: 1.8–2.2; pooled odds ratio)

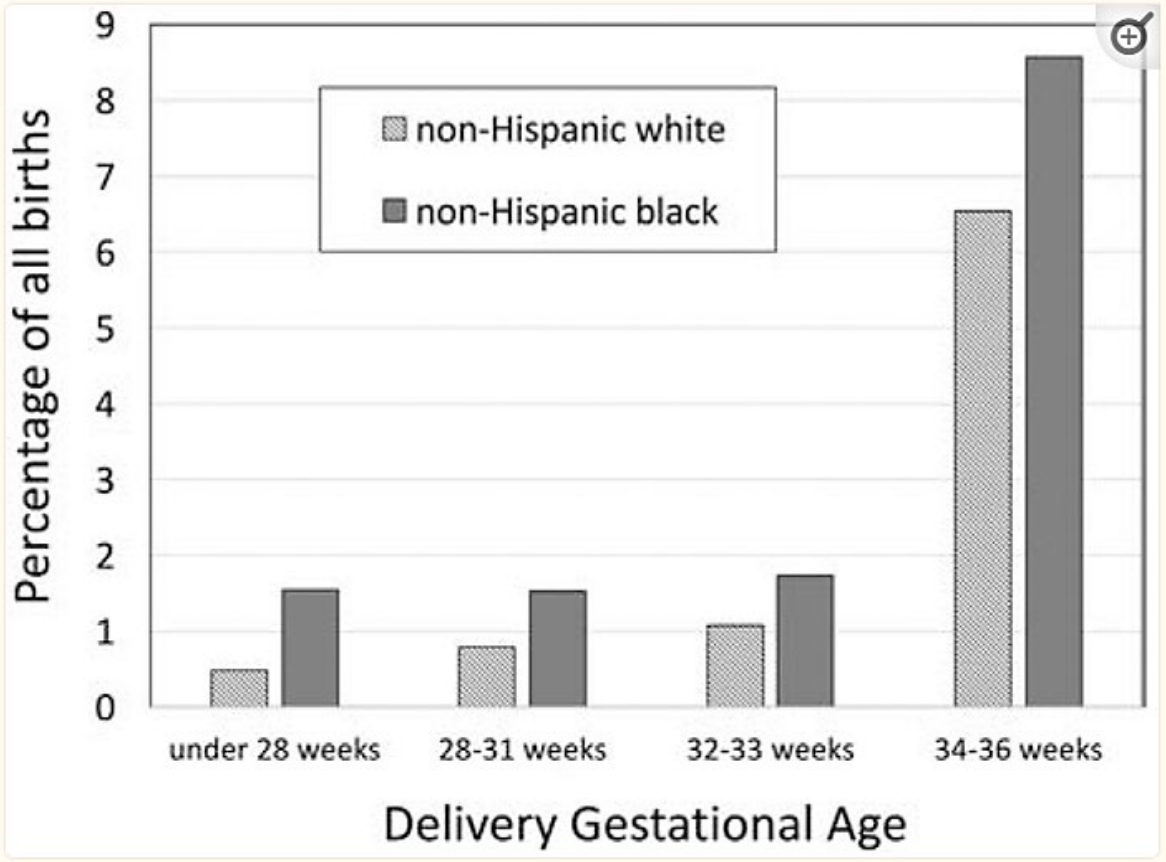
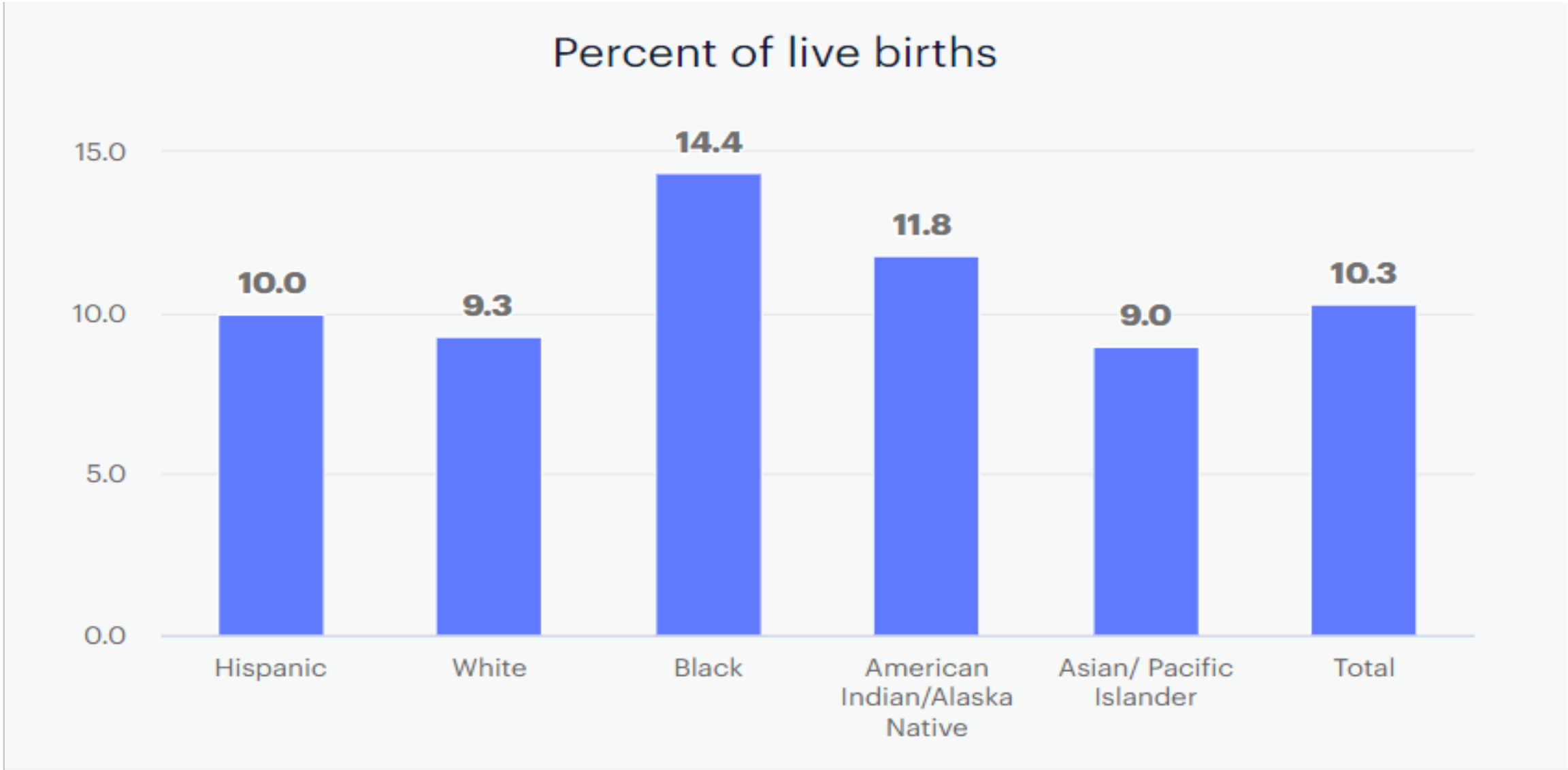



Fig. 1

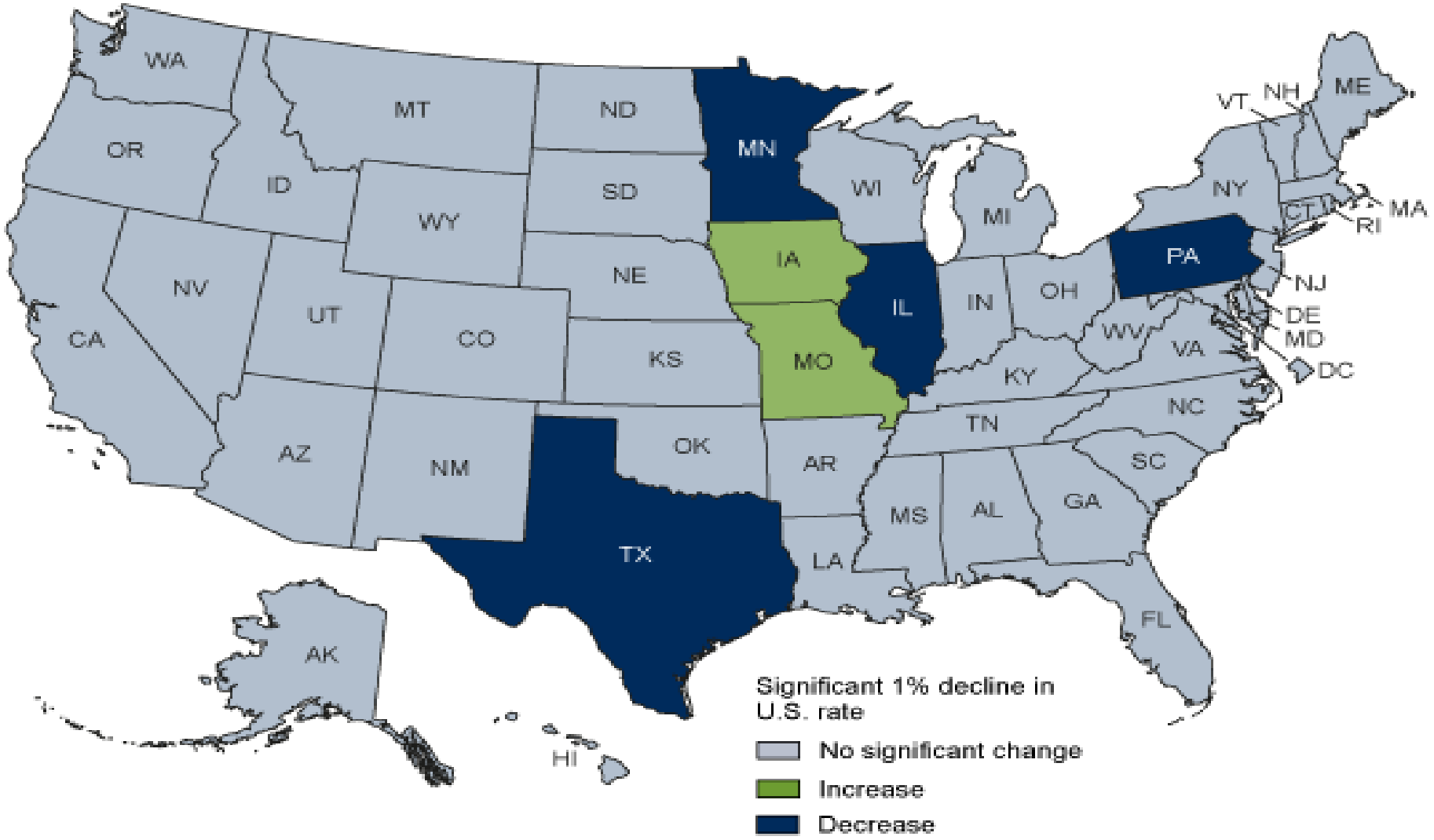
Proportion of preterm births, stratified by gestational age at delivery and maternal race, 2015. *Sources*: Martin et al. Final birth data 2015.

Manuck: Semin Perinatol. 2017 Dec; 41(8): 511–518

# PRETERM BIRTH BY RACE AND ETHNICITY 2019-2021



# CHANGE IN SINGLETON PRETERM BIRTH RATES, BY STATE: UNITED STATES, 2019 AND 2020



# STRESS AND IMMUNE FUNCTION

*Chronic Stress* has been shown to:

- ↑ susceptibility / severity of infections
- Decrease response to vaccines
- Alter wound healing
- Increase reactivation of herpes viruses
- Alter # & function of WBC's
- Increase IL-6 & decrease IL-10
- Associated with Bacterial Vaginosis in pregnancy

Glaser R, Kiecolt-Glaser J. Stress-induced immune dysfunction: implications for health. Nature Reviews/Immunology 2005;5:243-51.

# SPECIFIC HYPOTHESES ON STRESS AND PREMATURITY

Preterm birth will occur more commonly in women with perceived stress, who have biological markers of stress and of altered inflammation.

These women will more commonly be African American and will more commonly have pro-inflammatory polymorphisms

African American women w/ PTD will have evidence of stress & altered inflammation

# PREVENTION OF PRETERM BIRTH: EPIGENETICS

Epigenetics -Ann Hum Genet. 2020 May; 84(3): 205–213

- Variation in both the maternal and fetal genome.
- Some evidence that risk alleles in mothers may be enriched for processes related to immunity and inflammation, and in the preterm infant, processes related to brain development.
- Environmental as well as genetic factors contribute to preterm birth gene-environment interaction

# PREMATURITY PREVENTION


The New York Times

U.S. Lags in Global Measure of Premature Births

Give this article 164

1672
Regnier de Graaf

1898
Louis-August Prenant & Gustav born

1905
Ernest Starling

1930's
Butenandt, Westphal, Slotta, Hartmann, Wettsstein

1934
Corner & Allen Wintersteiner

1935
Second International Conference on the Standardization of Sex Hormones, London

1939
Butenandt & Ruzicka

1940's
Russell Marker

1949
Georgeanna S. Seegar Jones

1950's
Csapo

Late 1970's Early 80's
"Modern progester one era"

Where we are now

# HISTORY OF PROGESTERONE

Progesterone – natural hormone produced by the ovaries

First noted in publication in 1672 with description of female reproductive tract

Louis –August and Gustav Born (1898) proposed corpus luteum as organ of secretion supporting the early embryo

Ernest Starling (1905) coined the term hormone

# HISTORY OF PROGESTERONE

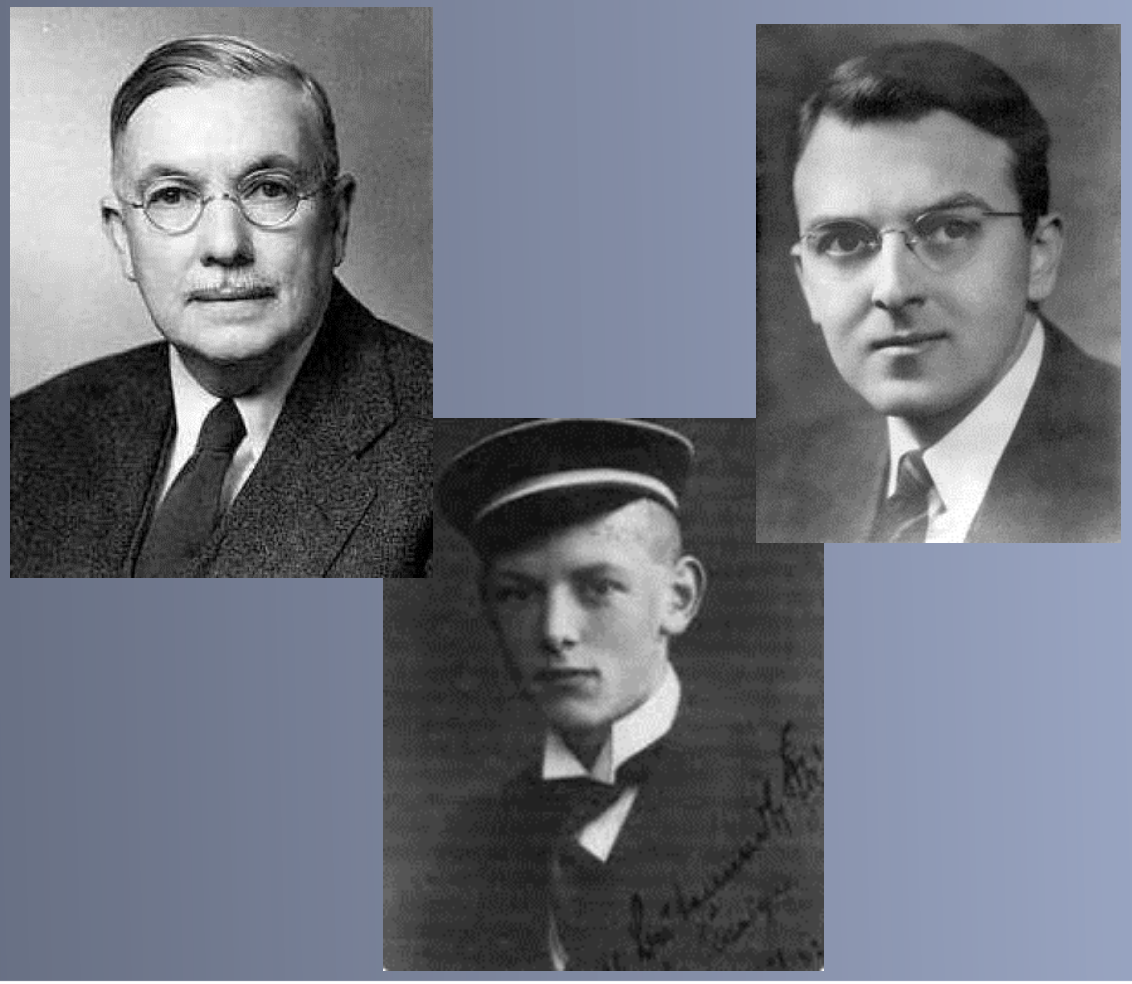
**Regnier de Graaf (1641-1673)**

- Dutch physician who discovered the follicles of the ovary (known as Graafian follicles), in which the individual egg cells are formed

**Louis August Prenant – 1898**

- Corpus Luteum a organ of internal secretion supporting implantation and the early embryo

# HISTORY OF PROGESTERONE



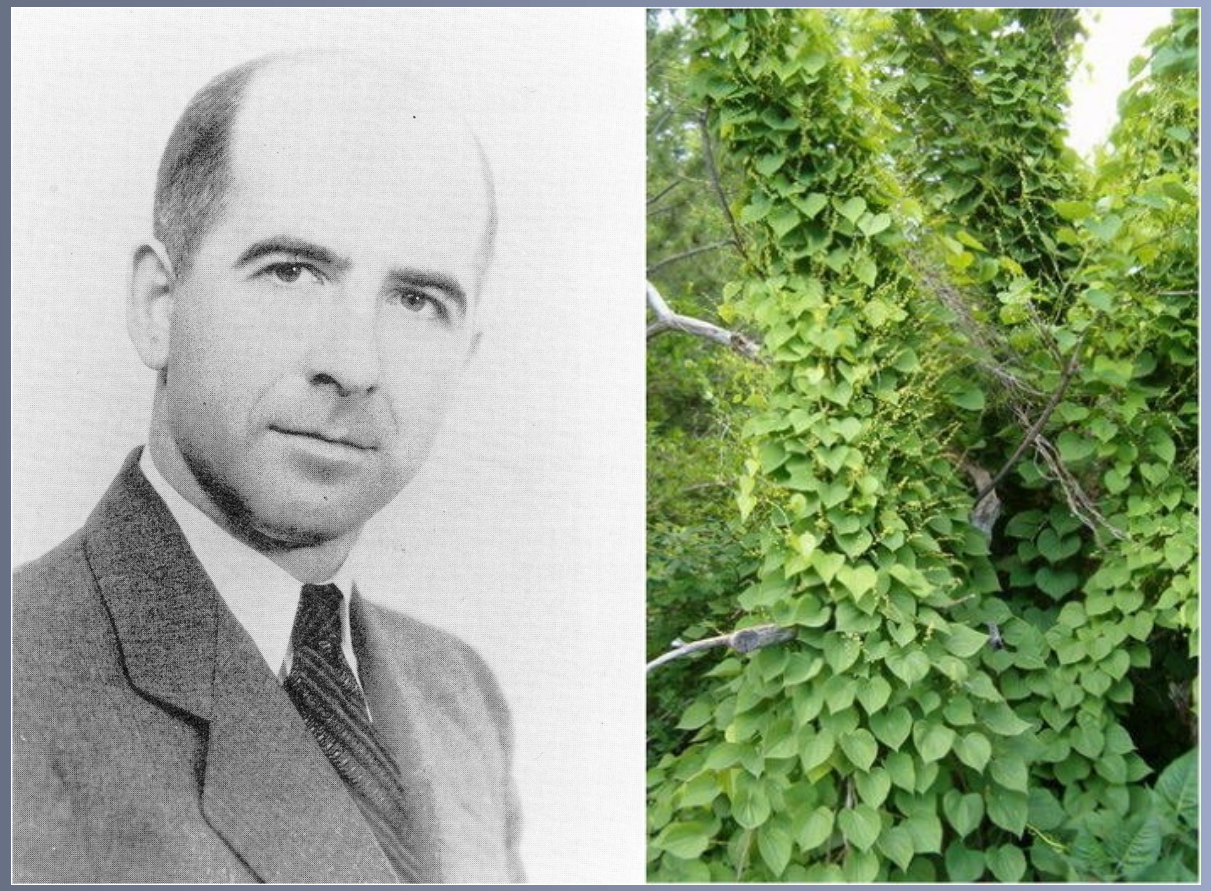
**<u>George W. Corner</u> and <u>Willard M. Allen</u>**

- Discovered the hormonal action of progesterone in 1929.

**<u>Adolf Butenandt</u> (German biochemist)**

- 1934, pure crystalline progesterone had been refined and obtained and the <u>chemical structure</u> of progesterone was determined
- 1939 -Received Nobel Prize

# HISTORY OF PROGESTERONE





**Russel Marker, American Chemist**

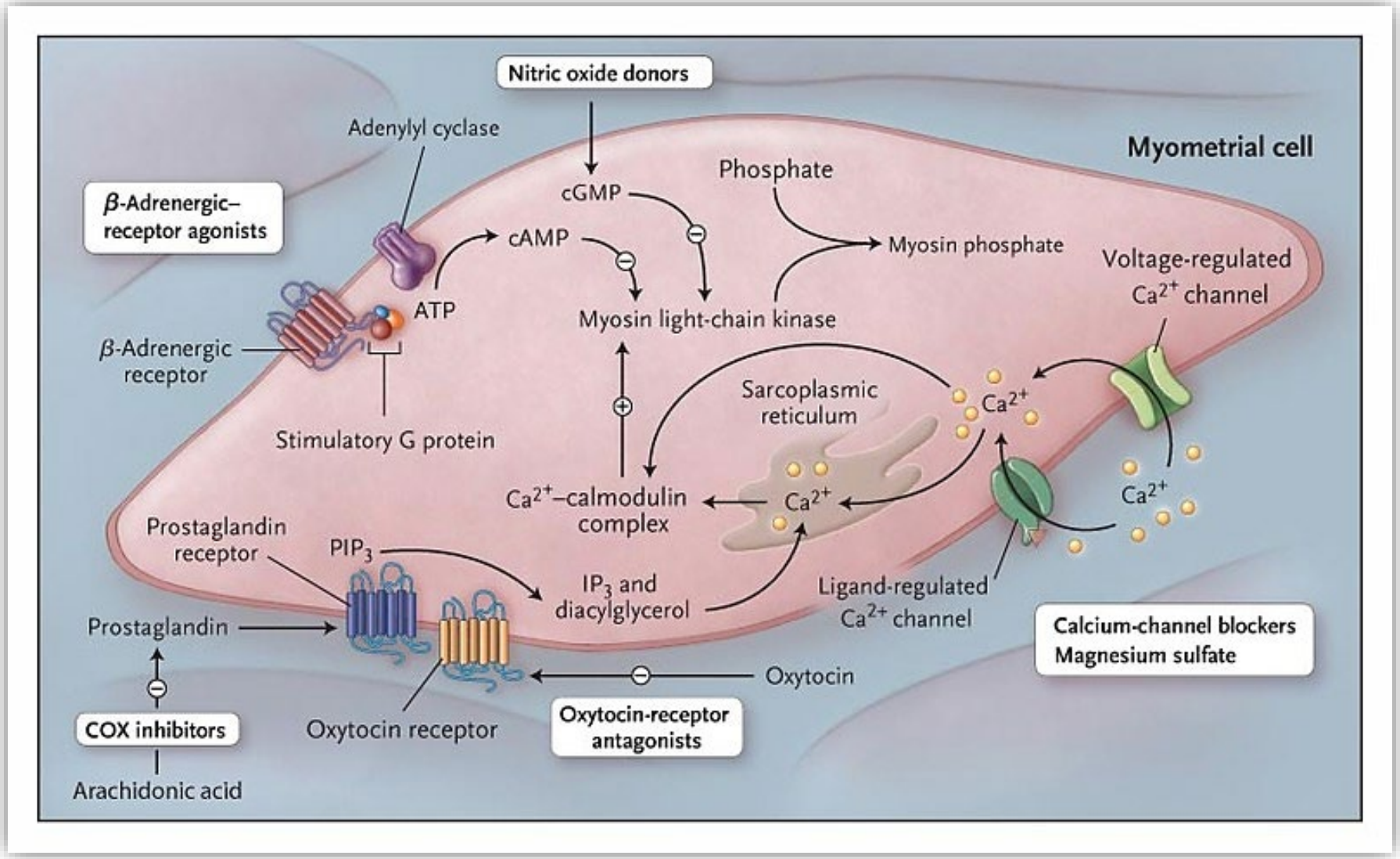
- 1944 Created Syntex the company used Mexican plant, Cabeza de Negro (*Dioscorea mexicana*), to create synthetic progesterone
- Dioscorea contains diosgenin
- First effective oral contraceptive

# HISTORY OF PROGESTERONE

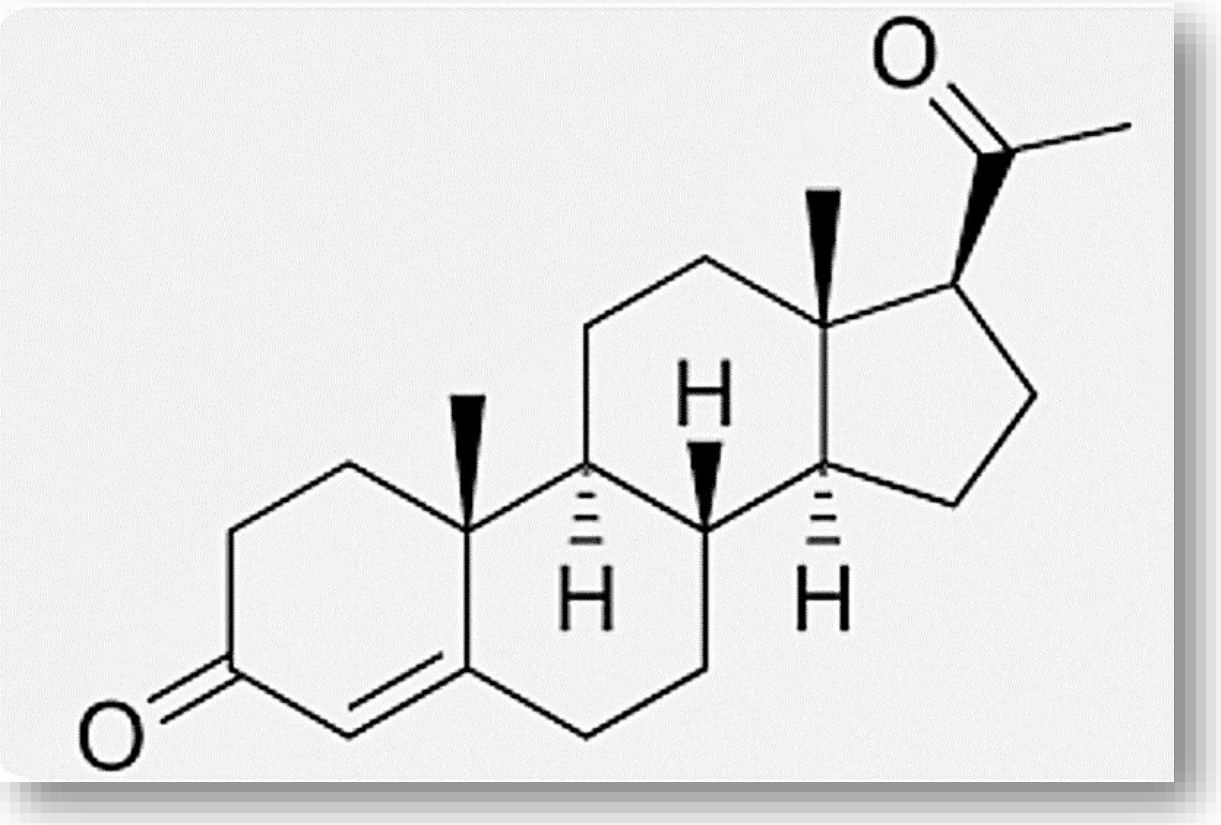
**Georgeanna S. Seegar Jones (1912-2005)**

- Described luteal phase deficiency
- Used progesterone to treat women with recurrent miscarriage.

# PREVENTION OF PRETERM BIRTH

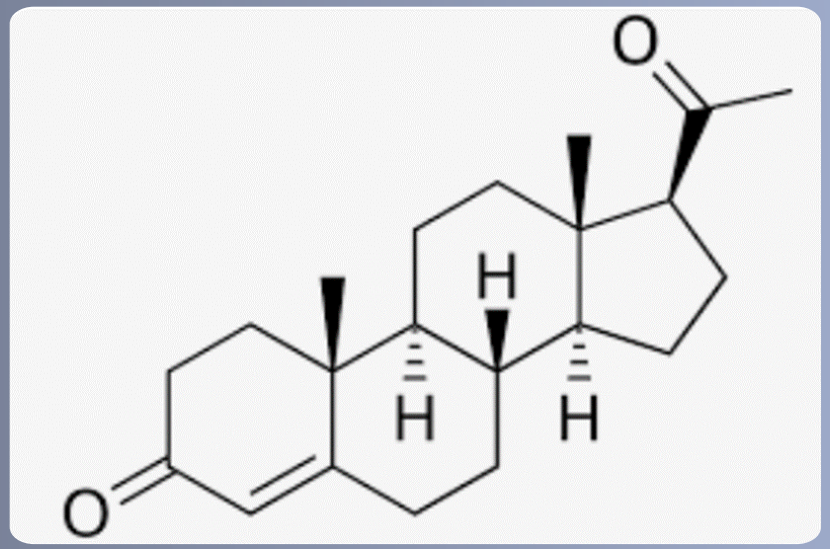


# PROGESTERONE (P4)




- 1933- Schering introduced progesterone in oil as first pharmaceutical formulation of progesterone and later micronization
- 1970- 1980's Micronization – allowed progesterone to be absorbed seven fold more efficiently orally described by Fitzpatrick
- Approval as oral capsule Urogestan ® 1980 and introduced in US 1998 and now marketed internationally
- Micronized progesterone elevates progesterone levels for 12 hours

# PROGESTERONE – MAINTENANCE OF PREGNANCY

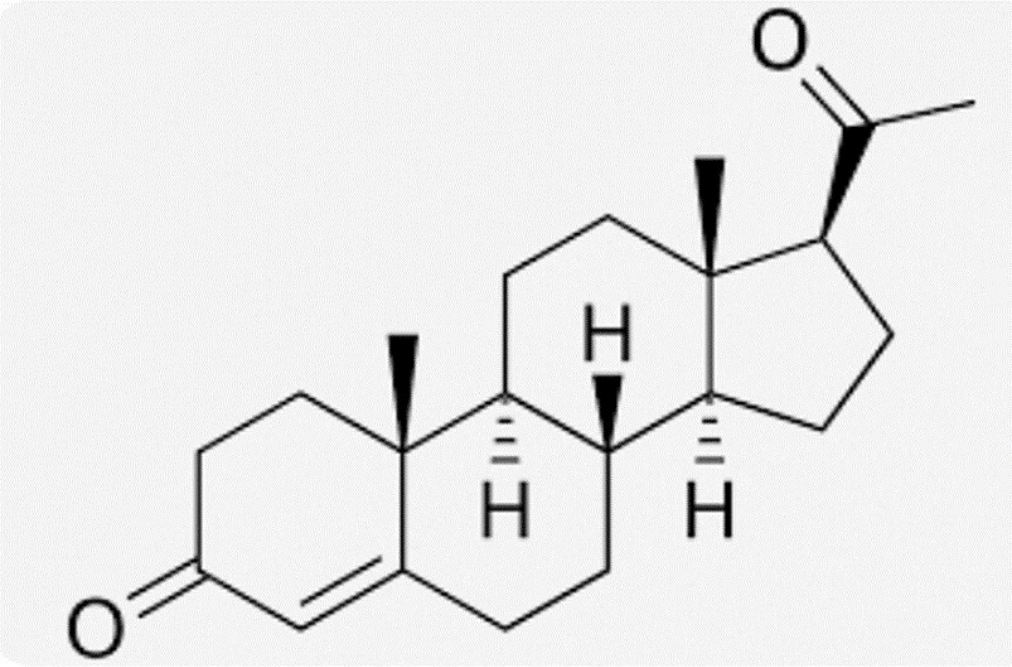



**Arpad Csapo (1918-1981)**

- Proposed P4 maintains pregnancy by blocking parturition mechanism and withdrawal leads to parturition
- Isolated actin and myosin responsible for contractility of uterine muscle and theorized that progesterone blocks that contractility

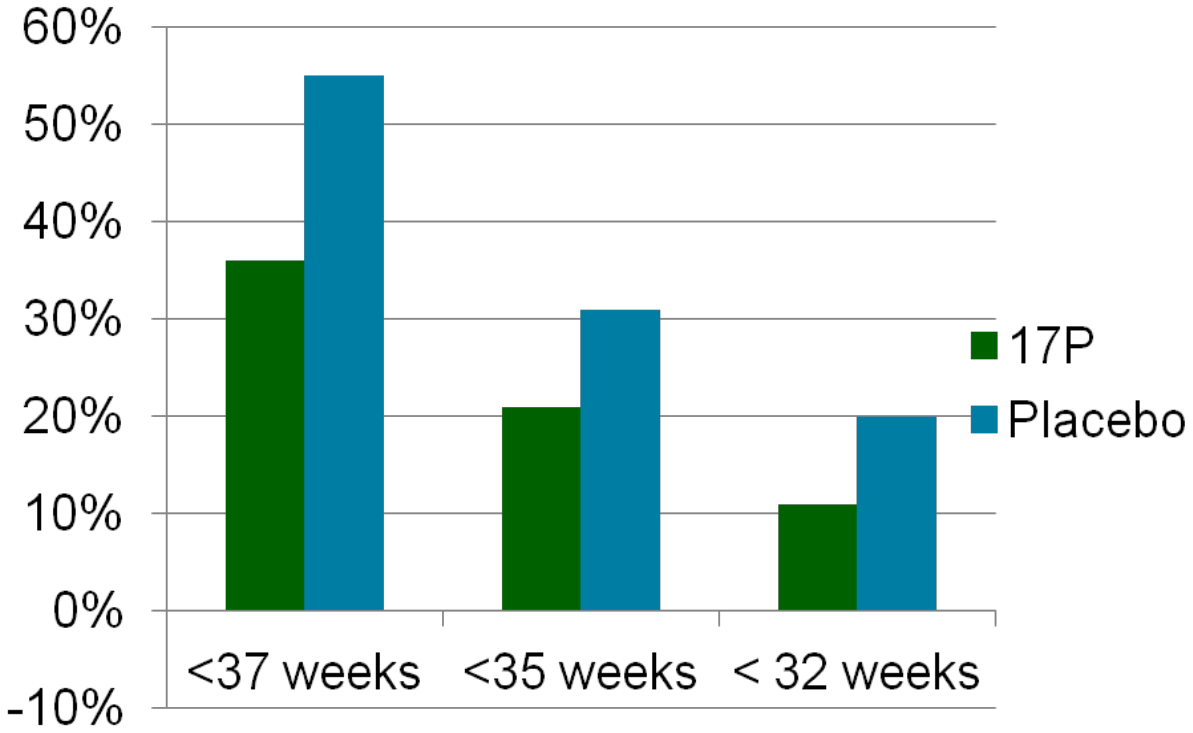
# PROGESTERONE FOR PREVENTION OF PRETERM BIRTH

- Progesterone in PTB prevention
- Proposed Mechanisms
  - lower prostaglandin synthesis
  - the inhibition of cervical stromal degradation
  - modulating the inflammatory response
  - reducing gap junction formation
  - decreasing myometrial activation.



# 2003: THE YEAR OF THE PROGESTINS

Meis et al, 2003, NEJM: MFMU trial randomized 459 women with prior sPTB to weekly IM 17P starting at 16-20 weeks, through 36 weeks gestation




# 17 HYDROXYPROGESTERONE : NEJM 2003

- 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.
- Primary outcome was preterm delivery before 37 weeks of gestation

ORIGINAL ARTICLE

## 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., et al., for the National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

**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) |

* Plus–minus values are means ±SD.
† P=0.007.
‡ Race was self-assigned by the women.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

**Table 2. Outcomes of Pregnancy According to Treatment Assignment.***

| 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) |
| Miscarriage at <20 wk of gestation | 5 (1.6) | 0 | NA |
| Hospital visit for preterm labor | 49 (16.0) | 21 (13.8) | 1.15 (0.72–1.86) |
| Tocolytic therapy | 53 (17.3) | 24 (15.9) | 1.09 (0.70–1.69) |
| Corticosteroids for fetal lung maturity | 52 (17.8) | 30 (19.7) | 0.91 (0.60–1.35) |
| Cesarean delivery | 77 (25.2) | 41 (26.8) | 0.94 (0.68–1.30) |
| Chorioamnionitis | 11 (3.6) | 5 (3.3) | 1.09 (0.39–3.09) |

* Data on hospital visit for preterm labor were missing for 1 woman in the placebo group; data on tocolytic therapy were missing for 2 women in the placebo group; and data on corticosteroids for fetal lung maturity were missing for 14 women in the progesterone group and 1 woman in the placebo group. CI denotes confidence interval, and NA not applicable.

# 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]

**Table 1** Demographic and clinical characteristics

| | 17-OHPC $n = 1,130$ | Placebo $n = 578$ |
|---|---|---|
| Maternal age (y) | 30.0 ± 5.2 | 29.9 ± 5.2 |
| Race | | |
| Black | 73 (6.5) | 41 (7.1) |
| Caucasian | 1,004 (88.8) | 504 (87.2) |
| Asian | 23 (2.0) | 22 (3.8) |
| Other | 30 (2.7) | 11 (1.9) |
| Hispanic or Latino ethnicity | 101 (8.9) | 54 (9.3) |
| No. of prior spontaneous PTB > 1 | 148 (13.1) | 70 (12.1) |
| Prior elective abortion | 281 (24.9) | 142 (24.6) |
| Prior indicated PTB | 19 (1.7) | 13 (2.3) |
| Gestational age at qualifying prior SPTB (wk) | 32 (28–35) | 33 (29–35) |
| Prepregnancy BMI ($kg/m^2$) | 23 (21–27) | 23 (21–27) |
| Marital status | | |
| Married/living with a partner | 1,013 (89.6) | 522 (90.3) |
| Never married | 86 (7.6) | 40 (6.9) |
| Divorced/widowed/separated | 31 (2.7) | 16 (2.8) |
| Years of education | 13 (11–15) | 13 (11–15) |
| Smoked during current pregnancy | 92 (8.1) | 41 (7.1) |
| Drank alcohol during current pregnancy | 24 (2.1) | 18 (3.1) |
| Used any "street drugs" during current pregnancy | 16 (1.4) | 8 (1.4) |
| Transvaginal cervical length <25 mm, $n/N1^a$ (%) | 10/833 (1.2) | 8/420 (1.9) |
| Prior vaginal progesterone therapy in pregnancy | 16 (1.4) | 10 (1.7) |

# 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]

**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) |

**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 |

# CONCLUSIONS
# PROLONG STUDY TO PREVENT RECURRENT PRETERM BIRTH (2019)

- No significant difference in frequency of PTB <35 weeks (11% vs. 11.5%)
- Neonatal morbidity index 5.6% v 5.0%
- Frequency fetal/early infant death (1.7% v 1.9%)
- 17 OHPC did not decrease recurrent PTD and was not associated with increased fetal/early infant death

# MAKENA (hydroxyprogesterone caproate injection)

- 2011
  - FDA approved Makena to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth
  - The FDA approved Makena under the accelerated approval pathway in 2011 based on a determination that the sponsor had demonstrated a drug effect on an intermediate clinical endpoint that was reasonably likely to predict clinical benefit.
  - Approval based on the results of a randomized, placebo-controlled trial of 463 women with a history of pre-term birth who received either hydroxyprogesterone caproate or placebo. Trial showed the drug reduced the risk of birth before 37 weeks but was not designed to assess whether hydroxyprogesterone caproate had a neonatal benefit.
- April 2023
  - FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena
  - Makena and its generics are no longer approved and cannot lawfully be distributed in interstate commerce

# Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial

Jane Elizabeth Norman, Prof, MD,[a,*] Neil Marlow, Prof, DM,[b] Claudia-Martina Messow, PhD,[c] Andrew Shennan, Prof, MD,[d] Phillip R Bennett, Prof, MD,[e] Steven Thornton, Prof, DM,[f] Stephen C Robson, Prof, MD,[g] Alex McConnachie, PhD,[c] Stavros Petrou, Prof, PhD,[h] Neil J Sebire, Prof, MD,[b] Tina Lavender, Prof, PhD,[i] Sonia Whyte, MSc,[a] and John Norrie, Prof, MSc[j], for the OPPTIMUM study group

## Table 2

Primary outcomes and their components for women entered into the treatment phase of the OPPTIMUM study and their babies

| | Placebo group | Progesterone group | Unadjusted odds ratio (95% CI) or difference in means (95% CI) | p value (unadjusted) | Adjusted odds ratio (95% CI)[*] or difference in means (95% CI) | p value (adjusted[*]) |
|---|---|---|---|---|---|---|
| Fetal death or delivery <34 weeks of gestation | 108/597 (18%) | 96/600 (16%) | 0·86 (0·64 to 1·17) | 0·34 | 0·86 (0·61 to 1·22) | 0·67 |
| Neonatal morbidity or death | 60/587 (10%) | 39/589 (7%) | 0·62 (0·41 to 0·94) | 0·02 | 0·62 (0·38 to 1·03) | 0·072 |
| Cognitive composite score at 2 years[‡‡] | 97·7 (17·5) | 97·3 (17·9) | −0·48 (−2·77 to 1·81)[§] | 0·68 | −0·48 (−2·77 to 1·81)[§] | 0·68 |
| Components of the obstetric outcome | | | | | | |
| Fetal death | 7/597 (1%) | 8/600 (1%) | 1·14 (0·41 to 3·17) | 0·8 | .. | .. |
| Liveborn delivery before 34 weeks | 101/590 (17%) | 88/592 (15%) | 0·85 (0·62 to 1·15) | 0·29 | .. | .. |
| Components of the neonatal outcome | | | | | | |
| Neonatal death | 6/597 (1%) | 1/600 (<1%) | 0·17 (0·06 to 0·49) | 0·0009[¶] | .. | .. |
| Bronchopulmonary dysplasia[‖] | 18/574 (3%) | 17/580 (3%) | 0·94 (0·49 to 1·78) | 0·84 | .. | .. |
| Brain injury on ultrasound scan[**] | 34/574 (6%) | 18/584 (3%) | 0·50 (0·31 to 0·84) | 0·008 | .. | .. |

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## Table 4

Secondary outcomes

| | Placebo group | | Progesterone group | | OR, HR, or mean difference (95% CI) | p value |
|---|---|---|---|---|---|---|
| | N | n (%) or mean (SD) | N | n (%) or mean (SD) | | |
| **Obstetric and neonatal** | | | | | | |
| Gestational age at delivery (weeks) | 597 | 36·8 (4·2) | 600 | 36·9 (4·1) | 1·03 (0·92 to 1·15) | 0·62 |
| Deaths up to 2 years of age | 509 | 16 (3%) | 500 | 20 (4%) | 1·28[*] (0·66 to 2·51) | 0·47 |
| Death after trial entry up to end of study | 598 | 16 (3%)[‡] | 600 | 20 (3%)[‡] | 1·26[*] (0·65 to 2·42) | 0·5 |

# PROGESTERONE FOR PRETERM BIRTH PREVENTION

EPPPIC meta-analysis included individual patient data from randomized trials of progestogens to prevent preterm birth, including 31 trials and 11 644 participants.-

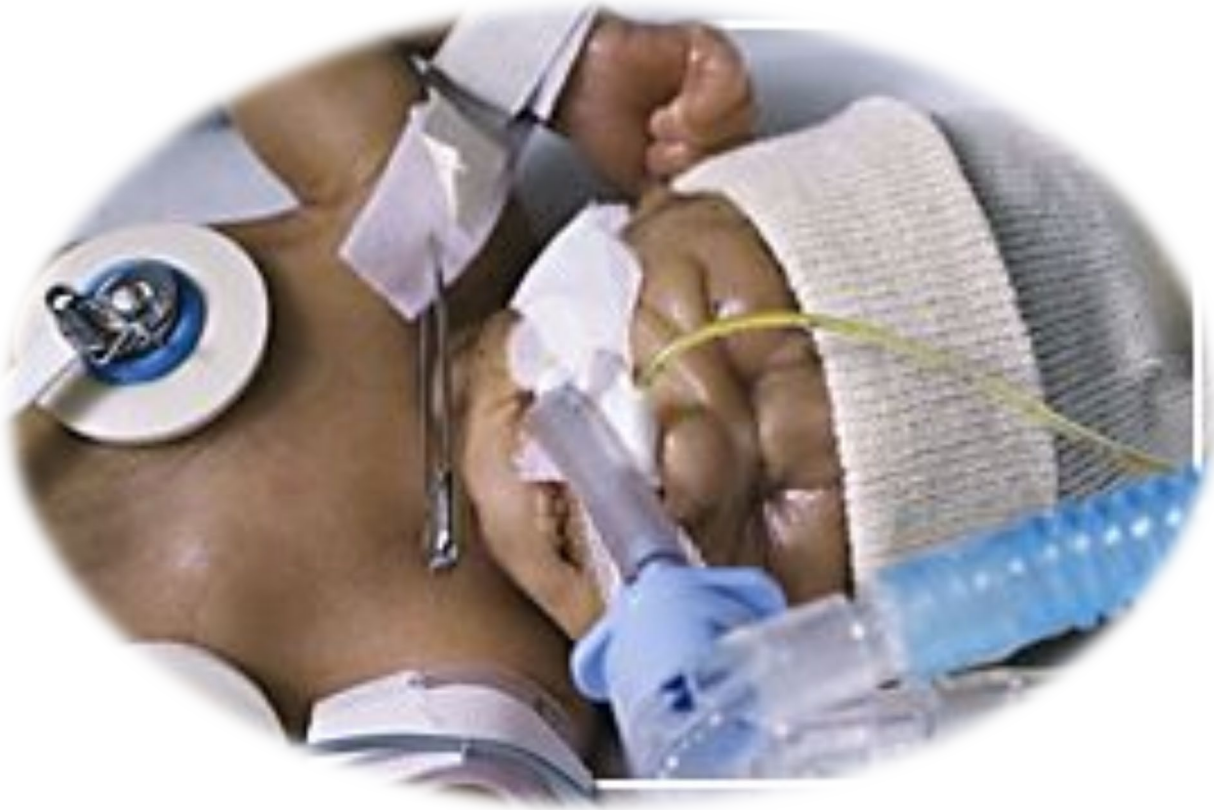
It demonstrated that both vaginal progesterone and 17-OHPC reduced the risk of preterm birth before 34 weeks for a high-risk population with singleton gestations

Benefit to those in original trials due to short cervical length (defined by different thresholds in different trials) or history of preterm birth (vaginal progesterone: 9 trials, 3769 women; relative risk [RR] 0.78, 95% CI 0.68–0.90; 17-OHPC: 5 trials, 3053 women; RR 0.83, 95% CI 0.68–1.01)

- Int J Gynaecol Obstet. 2021 Oct; 155(1): 16–18.

# PRETERM PROM

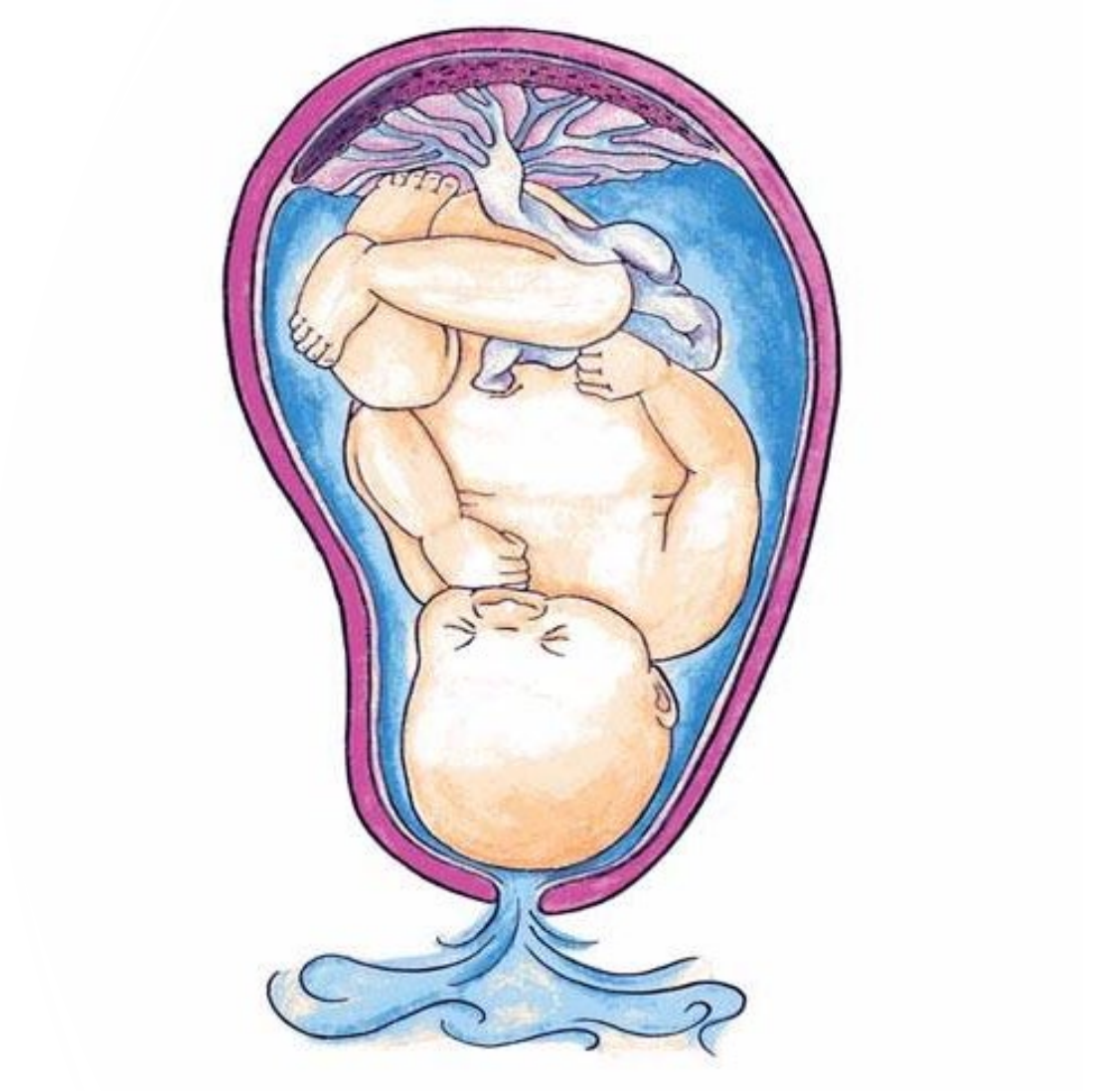
- Incidence 2-3% of all pregnancies
  - 20% of all perinatal deaths
- 120,000 pregnancies in the US per year
- 30-40% of all preterm neonates are result of PPROM



# ETIOLOGY OF PPROM

- Only 27% of PPROM patients have documentable infection at the time of rupture of membranes

- 73% have no evidence of infection at the time of PPROM



- Shen AJOG 2008;199:373.e7

TABLE 3

**Multivariable analysis for PPROM in black compared to white women**

| Birth outcome | n | Unadjusted RR (95% CI) | Adjusted[a] OR (95% CI) |
|---|---|---|---|
| All births (n = 644,462) | | | |
| Births ≥ 35 wk | 638,211 | Reference | Reference |
| PPROM < 35 wk[b] | 6234 | 2.73 (2.59-2.87) | 2.25 (2.04-2.49) |
| PPROM and late PTB (32-34)[c] | 3303 | 2.26 (2.09-2.43) | 1.94 (1.64-2.29) |
| PPROM and very PTB (28-31)[c] | 1685 | 3.19 (2.88-3.52) | 2.52 (2.26-2.80) |
| PPROM and extreme PTB (20-27) [c] | 1246 | 3.76 (3.35-4.21) | 2.82 (2.50-3.19) |
| Siblingships of singleton births to multiparous mothers (n = 148,378) | | | |
| Recurrent births ≥ 35 wk | 146,152 | Reference | Reference |
| Recurrent PPROM < 35 wk[d] | 91 | 7.20 (4.75-10.91) | 6.43 (3.74-11.04) |
| Isolated PPROM < 35 wk[d] | 2128 | 2.80 (2.55-3.07) | 2.10 (1.86-2.36) |

# RISK OF RECURRENT SPONTANEOUS PRETERM BIRTH: A SYSTEMATIC REVIEW AND META-ANALYSIS

- 32 articles involving 55 197 women
- The risk of recurrence due to preterm premature rupture of membranes (PPROM) at <37 weeks gestation was 7% (95% CI 6% to 9%),
- Risk of recurrence due to preterm labor (PTL) at <37 weeks gestation was 23% (95% CI 13% to 33%).

BMJ 2017; 7(6): e015402

# PREVENTION OF PRETERM BIRTH

- Selective Progesterone receptor modulator prevents systemic inflammation mediated preterm birth in mice
  - Promegestone (SPRM) binds progesterone receptors and is not metabolized by 20 a-hydroxysteroid dehydrogenase leading to suppression of term parturition and systemic bacteria – endotoxin induced preterm birth in mice

**TABLE 3**

**PMG blocks LPS-induced PTB, whereas progesterone reduces the incidence of preterm labor in mice**

| Outcome measures | LPS+vehicle | LPS+P4 | LPS+PMG |
|---|---|---|---|
| Preterm birth (number of dams) | 6/6 | 2/5 | 0/6 |
| Term birth (number of dams) | 0 | 3/5 | 1/6 |
| Postterm (number of dams) | 0 | 0 | 5/6 |
| Prevented preterm birth (%) | 0 | 60 | 100 |

Data are presented as number and percentage.

*LPS*, lipopolysaccharide; *PTB*, preterm birth; *P4*, progesterone; *PMG*, synthetic progestin.

*Shynlova et al. Promegestone delays preterm labor in mice. Am J Obstet Gynecol 2022.*

**Table 2.** Pharmacodynamic identikit of progesterone in pregnancy maintenance [26–32].

| Biochemical, Immune and Hormonal Effects | + | − |
|---|---|---|
| Maternal immune responses modulation (fetus as semiallogenic transplant—needs protection) | + | |
| Utero-placental perfusion changes and improvements | + | |
| Myometrial/uterine relaxation through: | + | |
| -Estrogen receptors (ER-alpha) expression | | − |
| -Estrogen sensitivity | | − |
| -Oxytocin receptors antagonization | | − |
| -Levels of cyclic adenosine mono phosphate (cAMP) | + | |
| -Nitric oxide synthetase (NOS) | + | |
| -Formation of myometrial gap junctions (channels made of connexin 43) | | − |
| Cervix integrity promotion | + | |
| Suppression of fetal immunoplacental inflammatory response | + | |
| Cervix ripening | + | |
| CRH (corticotrophin releasing hormone) and cortisol levels | | − |
| Prostaglandins release | | − |
| Vaginal microbiota influence (for vaginal administration) | + | |

# FACTORS INCREASING VULNERABILITY OF BLACK WOMEN TO PREMATURITY

- Biology, Genetics
  - Candidate genes
- Social
- Economic
- Behavioral
- Environmental
- Medical

**Table 1. Screening and Interventions for Prevention of Preterm Birth From the American College of Obstetricians and Gynecologists Practice Bulletin Published in August 2021**

| Cervical length ultrasound | IM 17-OHPC | Vaginal progesterone | Ultrasound-indicated cerclage | Physical examination–indicated cerclage | Cervical pessary |
|---|---|---|---|---|---|
| Singleton pregnancy, no prior preterm birth<br><br>Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment | Not indicated | Recommended for cervical length less than 25 mm | Insufficient data; possibly of benefit if the cervical length is less than 10 mm | Consider | Not indicated |
| Singleton pregnancy, prior spontaneous preterm birth<br><br>Serial (every 1–4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation | Offer progesterone supplementation (either 17-OHPC or vaginal progesterone) | Offer progesterone supplementation (either 17-OHPC or vaginal progesterone) If not on progesterone already, consider with a cervical length less than 25 mm (versus cerclage) | Consider with a cervical length less than 25 mm (versus vaginal progesterone if not already on progesterone supplementation) | Consider | Not indicated |
| Multiple gestation<br><br>Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment | Not indicated | Insufficient data | Insufficient data | Consider | Not indicated |

Abbreviations: IM, intramuscular; 17-OHPC, 17-α hydroxyprogesterone caproate.

Prior spontaneous preterm birth means that the patient had a prior singleton spontaneous preterm birth between 20 and 36 6/7 weeks[2] or a spontaneous preterm birth of twins between 20 and 33 6/7 weeks, which appears to impart a similar risk.[70]

Reprinted from Prediction and prevention of spontaneous preterm birth. ACOG Practice Bulletin No. 234. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;138:e65–90. doi: 10.1097/AOG.0000000000004479 [14]

# UPDATED CLINICAL GUIDANCE ACOG (2023)

- Vaginal progesterone may be considered as a treatment option for patients with a history of preterm birth, singleton gestation, and a shortened cervix. However, vaginal progesterone has not been proven effective in the absence of a shortened cervix and should not be considered as an alternative to 17-OHPC.
- Intramuscular 17-OHPC is not recommended for the primary prevention of preterm birth in patients with a history of spontaneous preterm birth.
- Dependent upon cervical length measurement, prior pregnancy history, and past treatment, a discussion of the range of interventions available to prevent a recurrent preterm birth should occur and a collaborative action plan should be developed.

ACOG Practice Bulletin No. 234 2021

# CURRENT PREVALENCE OF APPROPRIATE 17P USE?