Prematurity Disparity: Epidemiology, Intervention, Prevention

Developed in collaboration

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Learning Objective

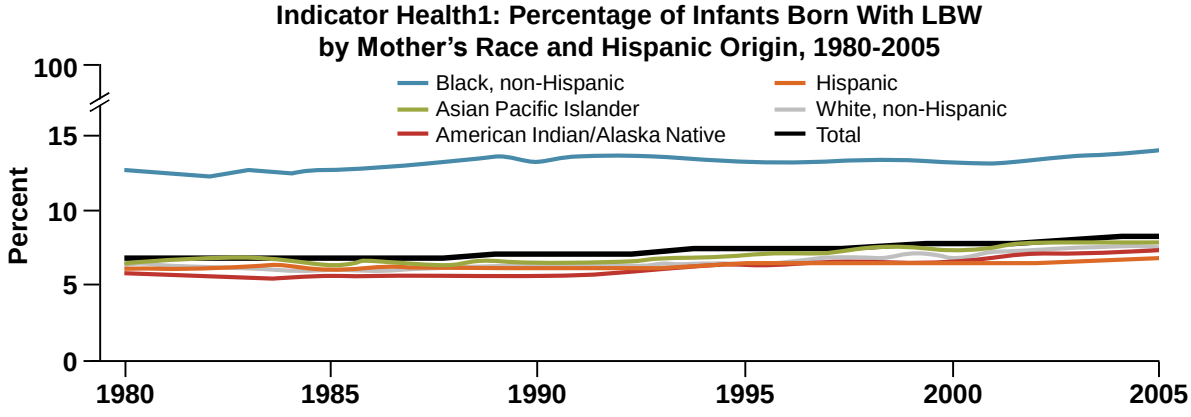
Upon completion, participants should be able to:

- Discuss the complex epidemiology and racial disparity of preterm birth and their impact on treatment, prevention, and long-term health

Preterm Birth: Exploring the Controversies

- Can preterm birth be prevented?
- Can preterm labor be stopped?
- Can perinatal morbidity and mortality from preterm birth be eliminated?
- Can the prematurity racial disparity gap be closed?

Prematurity: LBW by Race



Note: Data for 2005 are preliminary. Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.
Hamilton BE, et al. *Natl Vital Stat Rep*. 2006;55:1-18.

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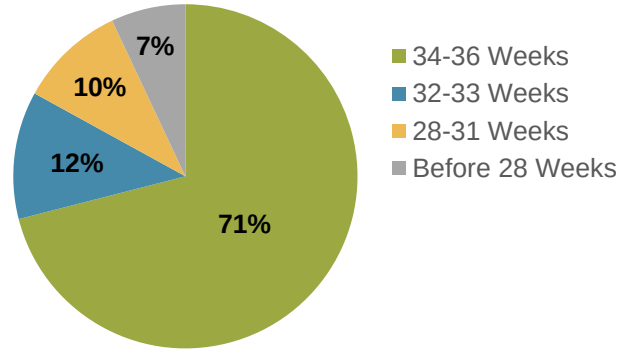
Prematurity Prevention

- Why has there been no improvement in preterm birth?
  - What causes labor?
  - What causes preterm labor?
- What models should direct strategies for prematurity prevention?
- What issues are unique to the US?

Premature Births in the US

- Babies born before 32 weeks of gestation face the greatest risk



Hamilton BE, et al. *Natl Vital Stat Rep*. 2015;64:1-64.

Factors Increasing Vulnerability of Black Women to Prematurity and LBW

Complex epidemiology and social determinates:

- Biology/genetics
- Social factors
- Economic factors
- Behavioral factors
- Environmental factors
- Issues related to medical care (quality, biases)

Bryant AS, et al. *Am J Obstet Gynecol.* 2010;202:335-43.

Specific Hypotheses on Stress and Prematurity

- Preterm birth occurs more commonly in women with perceived stress, who have biological markers of stress and altered inflammation
- These women are more commonly African American and more commonly have proinflammatory polymorphisms
- African American women with PTSD have evidence of stress and altered inflammation

Giurgescu C, et al. *Newborn Infant Nurs Rev*. 2013;13:171-7.

Recurrent Preterm Delivery

- Birth statistics
  - 3,988,076 births in the US each year
  - 10% of women deliver before 37 weeks (~398,000)
  - 59,000 born to mothers of a previous preterm infant
  - Majority born between 28-36 weeks
  - Pre-term delivery is the single most important predictor of perinatal mortality and morbidity
  - No change in the rates of pre-term delivery over the last 30 years
  - Bottom line: If delivery is < 32 weeks, long-term morbidity is greater

Hamilton BE, et al. *Natl Vital Stat Rep*. 2015;64:1-64; Mazaki-Tovi S, et al. *Semin Perinatol*. 2007;31:142-58.

Prevention of Prematurity

- Progesterone therapy
  - Randomized NICHD MFMU Network Trial
  - Weekly injections of 17P 250 mg IM vs placebo
  - Women with a documented history of previous spontaneous preterm birth < 37 weeks from 19 centers enrolled between 16-20 weeks

Meis PJ, et al. *N Engl J Med*. 2003;348:2379-85.

Pregnancy Outcomes ± Progesterone

	17P	Placebo	RR	95% CI	*P* Value
Delivery	n = 310	n = 153			
< 37 weeks	36.3%	54.9%	0.66	0.54-0.81	.001
< 35 weeks	20.6%	30.7%	0.67	0.48-0.93	.02
< 32 weeks	11.4%	19.6%	0.58	0.37-0.91	.02
Hospital visit for preterm labor	16.0%	13.8%	1.15	0.72-1.86	NS
Tocolytics	17.3%	15.9%	1.09	0.70-1.69	NS

Meis PJ, et al. *N Engl J Med*. 2003;348:2379-85.

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Therapy Candidates

- At risk of spontaneous preterm delivery (ie, documented history of a previous spontaneous birth at less than 37 weeks' gestation)
- Current pregnancy between 16-20 completed weeks
- Therapy continued until 36 completed weeks' gestation
- Safety considerations
  - Injection-site reactions were the most common adverse effect
  - 17P is contraindicated in patients with undiagnosed vaginal bleeding, history of or current thromboembolic disorders, liver dysfunction, breast cancer, and history of hypersensitivity to progestin
  - Decreased glucose tolerance may occur
- That is it!!

Meis PJ, et al. *N Engl J Med*. 2003;348:2379-85.

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Vaginal Progesterone* to Reduce Preterm Birth

- "Prophylactic administration of progesterone by vaginal suppository* to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study"
- "This is the first study that uses natural progestational agents"

*Off-label use.
da Fonseca EB, et al. *Am J Obstet Gynecol*. 2003;188:419-24.

Vaginal Progesterone* to Reduce Preterm Birth (cont.)

Materials and methods

- 142 asymptomatic high-risk singletons (PPTD, cerclage, or uterine malformation)
- Progesterone 100 mg vaginal suppository* every night (72) vs placebo (70) from 24-34 weeks' GA
- All women had UC monitoring once a week for 60 minutes at 24-34 weeks' GA

*Off-label use.
da Fonseca EB, et al. *Am J Obstet Gynecol*. 2003;188:419-24.

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Vaginal Progesterone* to Reduce Preterm Birth (cont.)

	Progesterone	Placebo	*P* Value
< 37 weeks	13.8%	28.5%	.03
34 weeks	2.8%	18.6%	.002
Admit with PTL	19.4%	31.4%	NS

- Average GAD: 33.5 progesterone group vs 32.0 placebo group for patients with PTD
- Safety considerations
  - Side effects are rare†
  - Vaginal progesterone is contraindicated in patients with undiagnosed vaginal bleeding, history of or current thromboembolic disorders, liver dysfunction, and breast cancer

*Off-label use.
†Adverse effects include abdominal pain and nausea; patients with a history of depression should be observed closely
da Fonseca EB, et al. *Am J Obstet Gynecol*. 2003;188:419-24.

Preterm Birth Prevention

- Long-term survival and preterm birth
  - Increased risk of mortality throughout childhood
    - For males born at 22 to 27 weeks, mortality rates were 1.33% and 1.01% for early and late childhood death, respectively (RR, 5.3 [95% CI, 2.0-14.2] and 7.0 [95% CI, 2.3-22.0])
    - For females born at 22 to 27 weeks, the mortality rate was 1.71% for early childhood death (RR, 9.7 [95% CI, 4.0-23.7]); no increased risk of late childhood death
    - Preterm women but not men were at increased risk of having preterm offspring
    - Reproduction diminished for index participants born preterm

Swamy GK, et al. *JAMA*. 2008;299:1429-36.

Preterm Delivery

Between 6%-12% of deliveries happen before 37 weeks

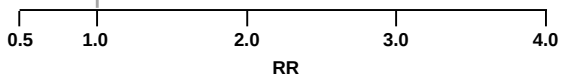
Hamilton BE, et al. *Natl Vital Stat Rep*. 2015;64:1-64.

For the 8% of deliveries associated with LBW (< 2,500 g), there is a TWO-FOLD INCREASE in **maternal** CVD and death

Rich-Edwards JW, et al. *Epidemiol Rev*. 2014;36:57-70.

Preterm Delivery and Risk of Maternal CVD

Reference (author, year)	RR (95% CI)	Mean or Median Years of Follow-Up
Davey-Smith, 2000	2.06 (1.22, 3.47)	30
Irgens, 2001	2.95 (2.12, 4.81)	13
Smith, 2001	2.10 (1.50, 3.00)	15-19
Davey-Smith, 2005	2.45 (2.06, 2.91)	20
Wikström, 2005	1.30 (1.10, 1.50)	19-28
Nardi, 2006	2.12 (1.19, 3.78)	Unknown
Catov, 2010	1.36 (1.31, 1.41)	28
Lykke, 2010	1.49 (1.36, 1.64)	14
Bonamy, 2011	1.68 (1.50, 1.88)	12
Hastie, 2011	1.58 (1.47, 1.71)	22



Rich-Edwards JW, et al. *Epidemiol Rev*. 2014;36:57-70.

Prematurity and Infant Mortality Disparity Unanswered?

- What factors in the lives of American black women are so hazardous to fetal and infant health?
- How does lower socioeconomic status translate into health disadvantages?
- Can health programs with a social as well as medical emphasis make a difference?

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Prevention of Prematurity and Preterm Disparities

- Primary prevention
  - Identify and manage risks and complex epidemiology
  - Implement a risk-reduction approach and strategies to improve reproductive health
  - Prevent PTL
- Secondary prevention
  - Prevent preterm delivery
- Tertiary prevention
  - Prevent/minimize complications of prematurity
- Quaternary prevention
  - Manage long-term health implications for those born preterm and those who deliver preterm

Institute of Medicine (US) Committee on Understanding Premature Birth and Assuring Healthy Outcomes; Behrman RE, Butler AS, eds. *Preterm Birth: Causes, Consequences, and Prevention*. 2007.

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Abbreviations/Acronyms
Prematurity Disparity

17P = 17-alpha hydroxyprogesterone caproate
CI = confidence interval
CVD = cardiovascular disease
IM = intramuscular
GA = gestation
GAD = gestational age at delivery
LBW = low birthweight
NICHD MFMU = National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network
NS = not significant
PPTD = previous preterm birth
PTD = preterm delivery
PTL = preterm labor
PTSD = posttraumatic stress disorder
RR = relative risk
UC = uterine contraction
US = United States