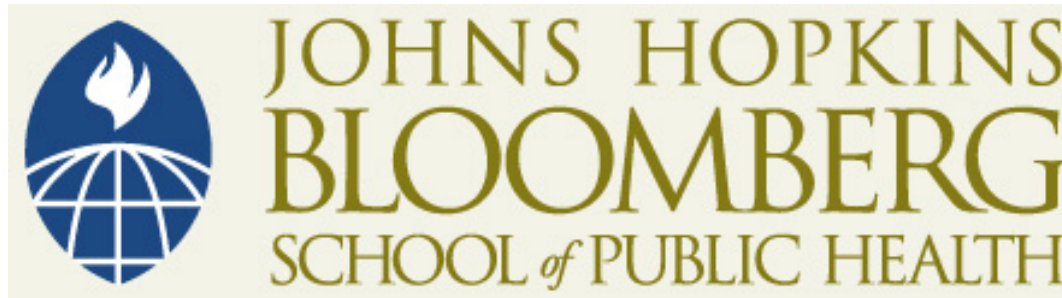


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Lecture 12

Epidemiology of Low Birth Weight, Preterm Delivery, and Intrauterine Growth Retardation I

Low Birth Weight (LBW)

- Birth weight < 2,500 grams
- Very low birth weight < 1,500 grams
- LBW results from two processes
 - **Shortened duration of pregnancy** (preterm birth)
 - **Intrauterine growth that is less than expected** for the length of gestation: intrauterine growth retardation (IUGR) or small for gestational age (SGA)]
- Multiple births have lower birth weights, so analyses must be stratified by singleton and multiple births

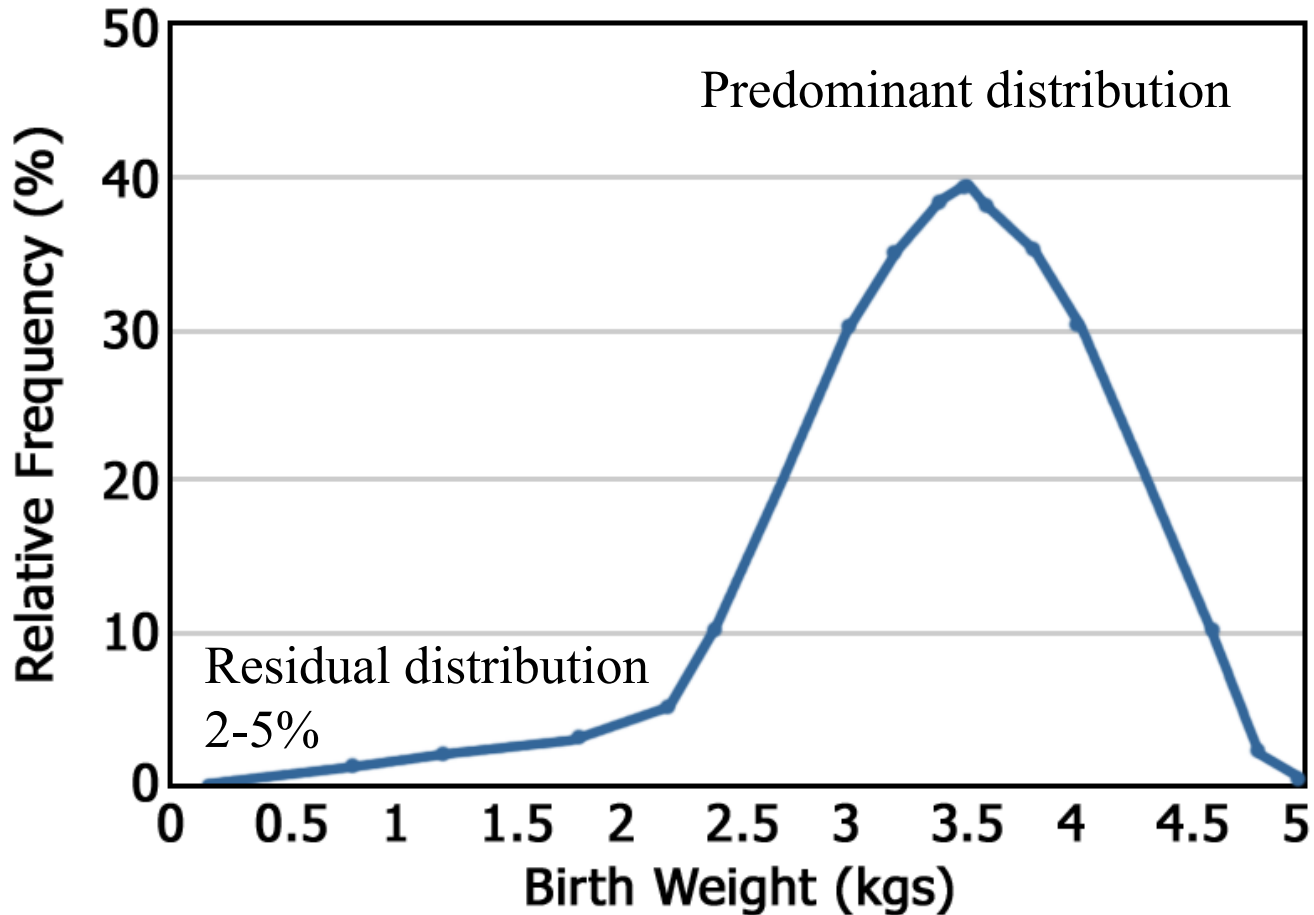
Birth Weight Measurement and use of Surrogate Measures

- Birth weight on day of birth
 - Weight drops postpartum due to neonatal diuresis, so it best measured on the day of birth
- Delayed observation (home deliveries in LDCs)
 - Cannot weigh infant on day of birth Use stable surrogate markers
 - Chest circumference <30 cm ~ wt $<2,500$ g
 - Head, calf, and mid-upper arm circumferences

Birth Weight and Intrauterine Growth Retardation

- **Observed birth weight (grams)**
- **Birth weight for gestational age**
- **Percentiles of BW by GA: < 10% small for gestational age (SGA)**
- **Z scores**

Distribution of Birth Weight in the U.S. Population



Note: 6% of births are LBW, 1% of births are VLBW

Proportional and Disproportional Intrauterine Growth Retardation

- **Proportional IUGR** - reduction in weight and length (symmetrical growth retardation, suggesting effects throughout pregnancy)
- **Disproportional IUGR** - reduction in weight more than length (growth retardation late in pregnancy)
- Measured by **Ponderal Index** (PI) = birth weight (g) /length (cm)³ x 100

Preterm Delivery

- Preterm < 37 completed weeks of gestation
- Very preterm <34 or <32 weeks (highest risk)
- **Measurement**
 - Fertilization (ART)
 - Last menstrual period (LMP)
 - Ultrasound
 - Maturity assessment of new born (Ballard, Dubowitz, Capurro scores). Combination of neuromuscular and developmental markers
- **Subtypes**
 - spontaneous preterm labor
 - preterm premature rupture of membranes (PROM)
 - induced preterm

Measurement of Gestational Age (GA)

- **Last Menstrual period (LMP)**
- Recall Errors
 - Vary by education, literacy, numeracy
- Women not menstruating
 - overestimate GA, underestimate PTD
 - lactating
 - recent spontaneous abortion
 - recent delivery
- Individual variability in length of menstrual cycle
 - Long cycles: underestimate GA, overestimate PTD?
 - Short cycles: overestimate GA, underestimate PTD?
- Bleeding during pregnancy
 - Underestimate GA (mistaken for LMP)

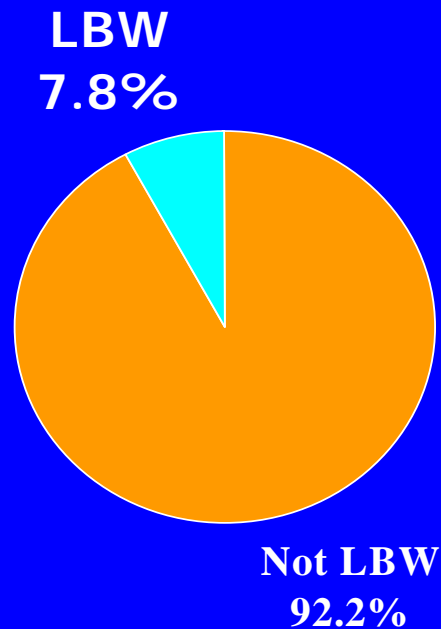
Classification of LBW/PTD

<u>GA</u>	<u>LBW</u>	<u>NORMAL BW</u>
≥ 37 weeks	IUGR	Normal
< 37 weeks	Preterm and/or IUGR	Preterm

PTD and IUGR as Determinants of LBW

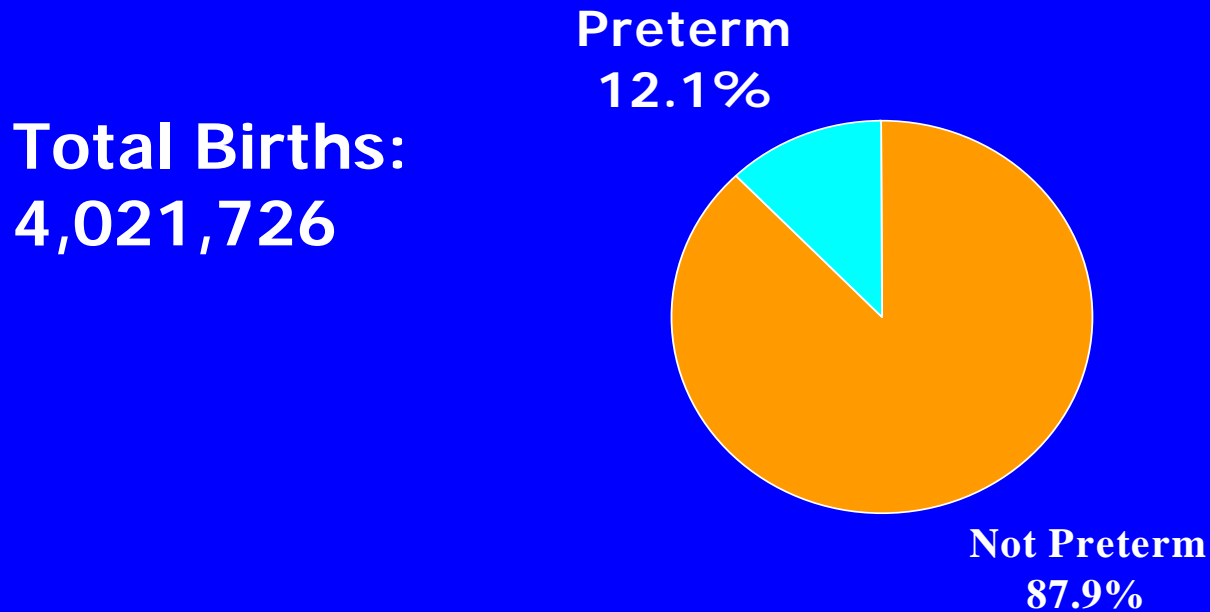
- LBW infant born at 40 weeks results from IUGR
- Preterm infant may be LBW, but have an appropriate weight for its gestational age
 - LBW only because it was born early
- Preterm infant may also be growth retarded
 - LBW because of both its shortened gestation and its growth retardation

Live Births by Birth Weight, U.S., 2002



Source: NCHS (2002), Final natality data

Live Births by Gestational Age, U.S., 2002



Source: NCHS (2002), Final natality data

Low Birth Weight Worldwide

- LBW = 16.4% in developing countries (20.5 million infants/year)
- Term LBW = 11% (13.7 million infants)
- IUGR = 23.8% (30 million infants)
- Distribution of burden:
 - 75% in Asia (mostly south-central Asia)
 - 20% in Africa
 - 5% in Latin America

Prevalence of LBW, IUGR and PTD in Developing Countries

	Argentina	Malawi	Nepal
LBW %	6.3	11.6	22.3
IUGR %	9.7	26.1	42.7
PTD %	7.2	8.2	21.8

WHO collaborative study of pregnancy outcomes, A. Kelly et al., 1996

Proportion of LBW due to PTD & IUGR: International Comparisons

- **Developed countries:** preterm 75%, IUGR 25%
- **Developing countries:** preterm 25%, IUGR 75%
- Based on meta-analysis of studies, mainly from Latin America, problematic measurement of gestational age
- **Africa (Rakai)**
 - All LBW 11.0%
 - LBW/IUGR 7.4%
 - LBW/PTD 3.6%
 - 67% IUGR, 33% PTD

Fetal growth in early pregnancy and LBW

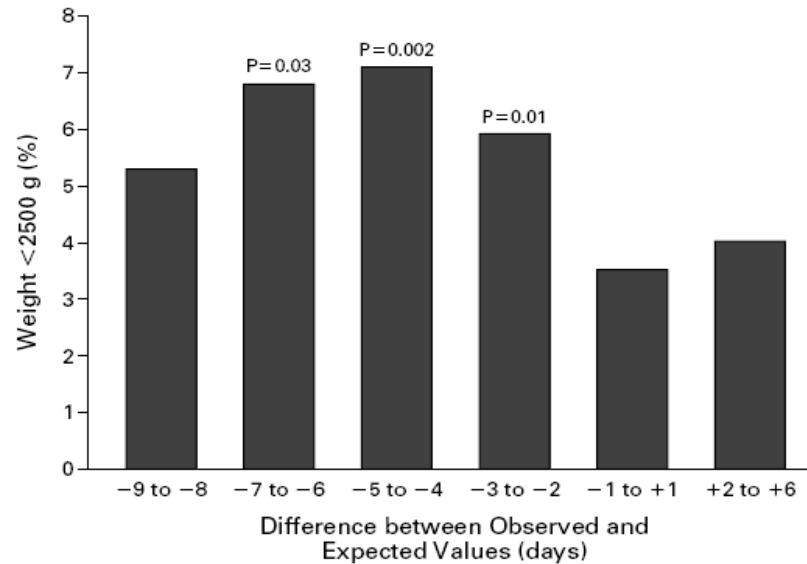
- Hypothesis that poor placental function in 1st trimester can cause LBW.
- Use crown-rump length based on ultrasound to estimate growth in the first trimester, in women with known dates of conception based on LMP or assisted reproduction (IVF, intrauterine insemination) expressed observed to expected days of gestation

Fetal growth in 1st trimester assessed by LMP and crown-rump length and outcomes at birth (Smith NEJM 1998;339:1817)

4229 singleton pregnancies with LMP and 1st trimester ultrasound

Outcomes	Adjusted OR (CI) associated with smaller than expected crown-rump length
LBW	1.7 (1.2-2.3)
SGA <5%	2.8 (1.9-4.3)
PTD 24-32 wk	2.0 (1.1-4.0)

1st trimester growth based on LMP and LBW



No. of INFANTS	
Weight < 2500 g	8 14 33 44 53 24
Weight ≥ 2500 g	142 191 429 705 1461 570

Figure 1. Proportion of Infants with Birth Weights of Less Than 2500 g According to the Difference between Observed and Expected First-Trimester Crown-Rump Lengths.

P values are for the comparison with the group with normal crown-rump length (-1 to +1 day) by Fisher's exact test (two-tailed). The proportion of infants with low birth weight in the pooled group for whom the difference was -9 to +6 days was not significantly different from the proportion of infants for whom the difference was less than -9 days (32 of 492; P=0.12) or greater than +6 days (2 of 63; P=0.77). The crown-rump length was expressed as equivalent days of growth.

Figure 1. Smith GCS, et al. First-Trimester Growth and the Risk of Low Birth Weight. NEJM;339:1817-1822. Copyright © 1998. Massachusetts Medical Society. All Rights Reserved.

SGA associated with lower 1st trimester growth in women with ART (Bukowski BMJ 2007)

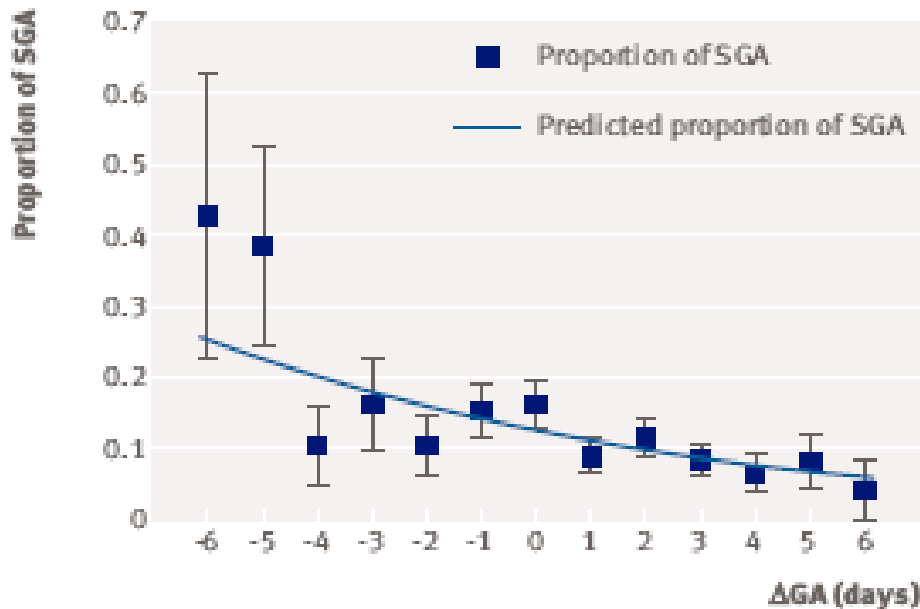


Fig 2 | Proportion of small for gestational age (SGA) neonates by size of ΔGA discrepancy (difference between observed and expected size of fetus in first trimester of pregnancy). Proportion ($\pm SE$) of SGA neonates and proportion of SGA neonates predicted by multivariable logistic regression are plotted by size of ΔGA discrepancy

Based on precise dates of Conception, poor fetal Growth in the 1st trimester Increased the risk of SGA

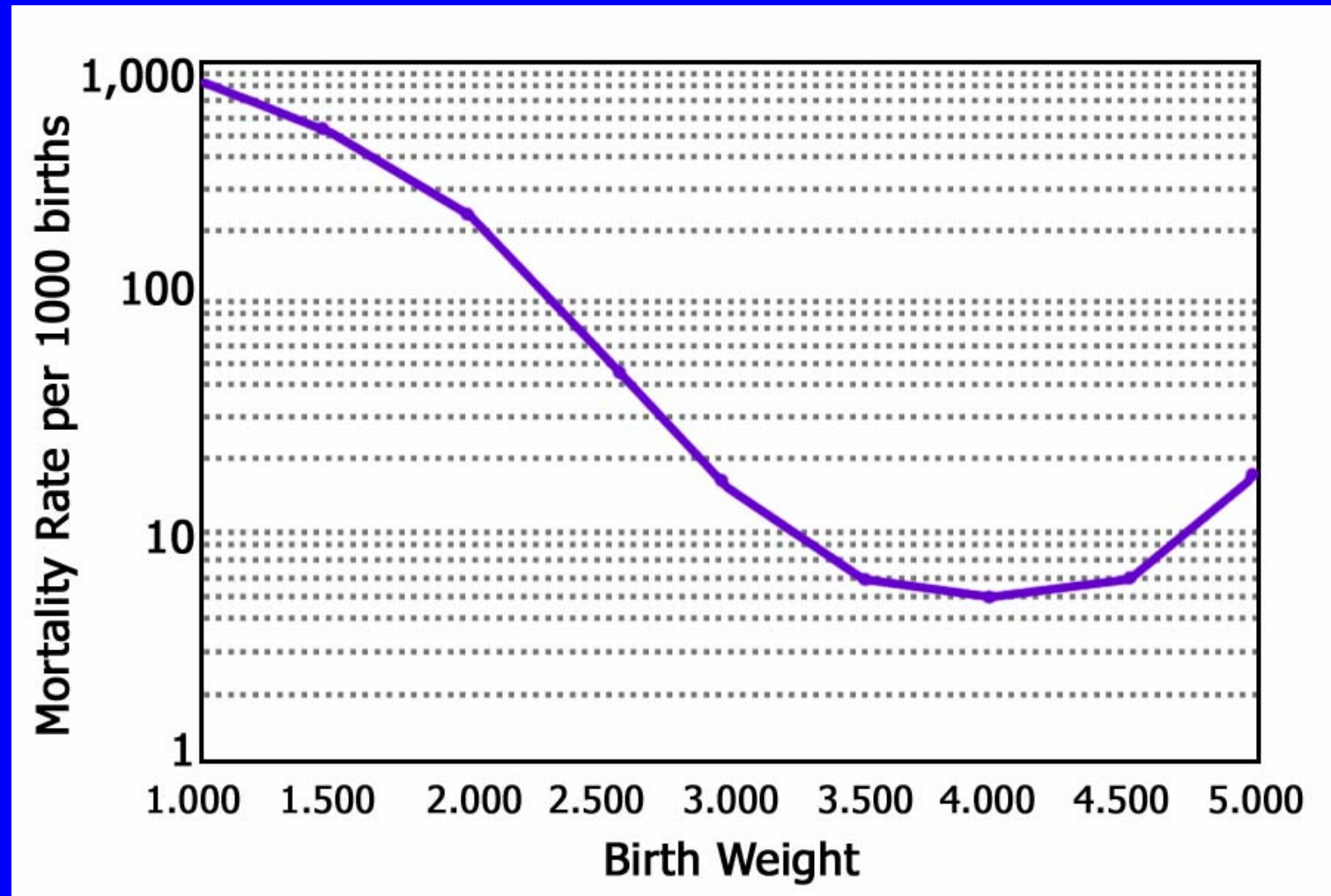
Birth Weight and Gestational Age Effects on Mortality and Morbidity

- Birth weight and gestational age are predictors of infant mortality
- **Low Birth Weight**
 - Moderate LBW infant mortality RR ~ 5 vs. normal birth weight
 - VLBW infant mortality RR ~ 100 vs. normal-weight infants
- **Preterm Delivery**
 - 70% of perinatal deaths are PTD
 - 50% of long-term neurologic morbidity is PTD
 - Most serious morbidity/mortality in PTD < 32 weeks and very low birth weight (VLBW < 1500 g)

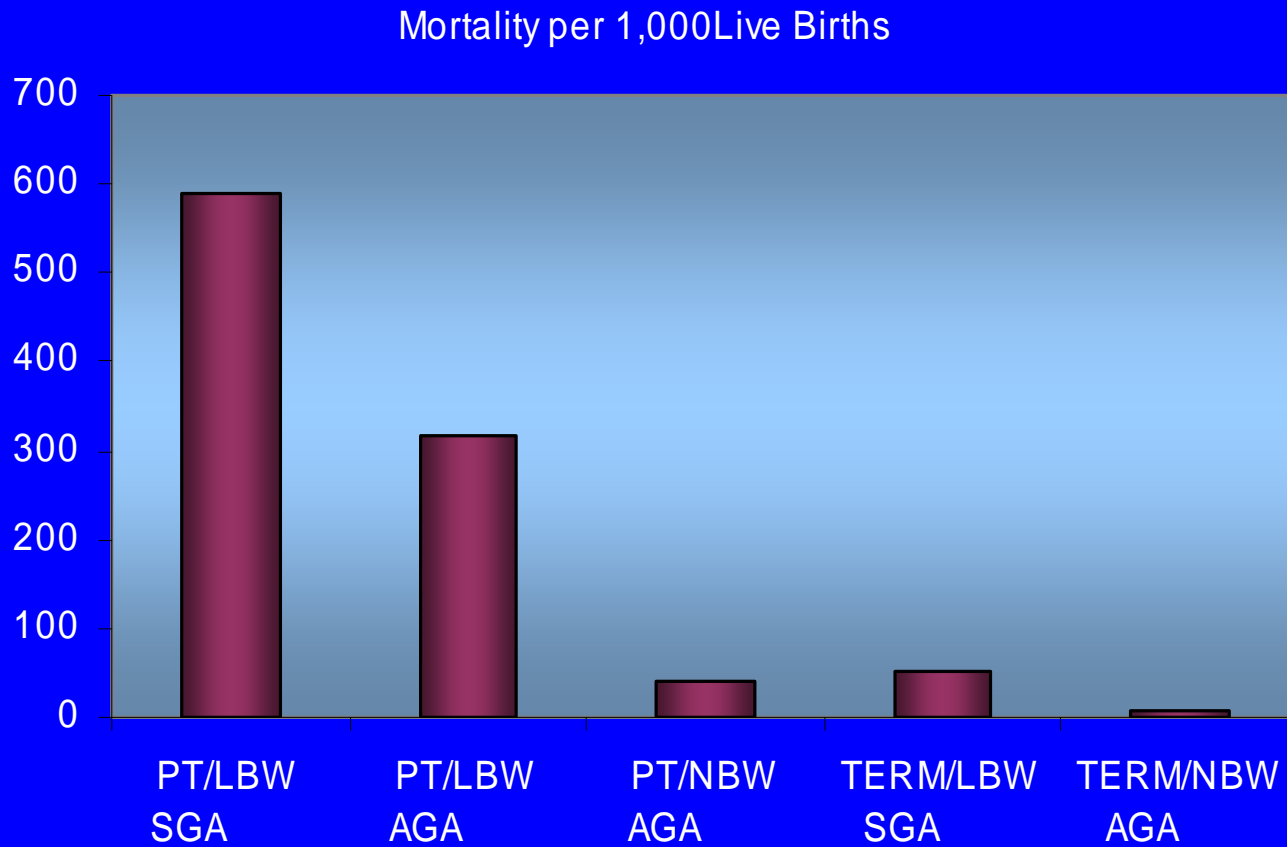
Birth Weight and Gestational Age Effects on Infant Mortality

- Are infants at high risk of dying because they are small or because they are preterm?
- Gestational age is in the causal pathway leading to birth weight

Birth Weight and Perinatal Mortality



Early Neonatal Deaths/ 100 Livebirths by PTD, LBW and SGA



Source: Gray RH, International Journal of Epidemiology 1991; 20(2): 467-73.

Birth Weight in Relation to Morbidity and Mortality Among Newborn Infants

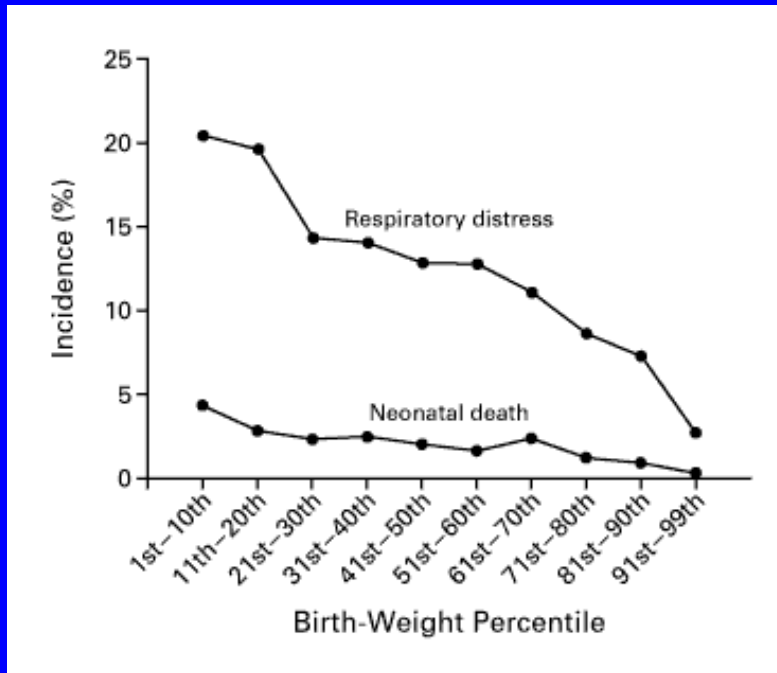


Figure 1. Incidence of Respiratory Distress and Neonatal Death among 12,317 Preterm Infants (Born at 24 to 36 Weeks of Gestation), According to Birth-Weight Percentile.

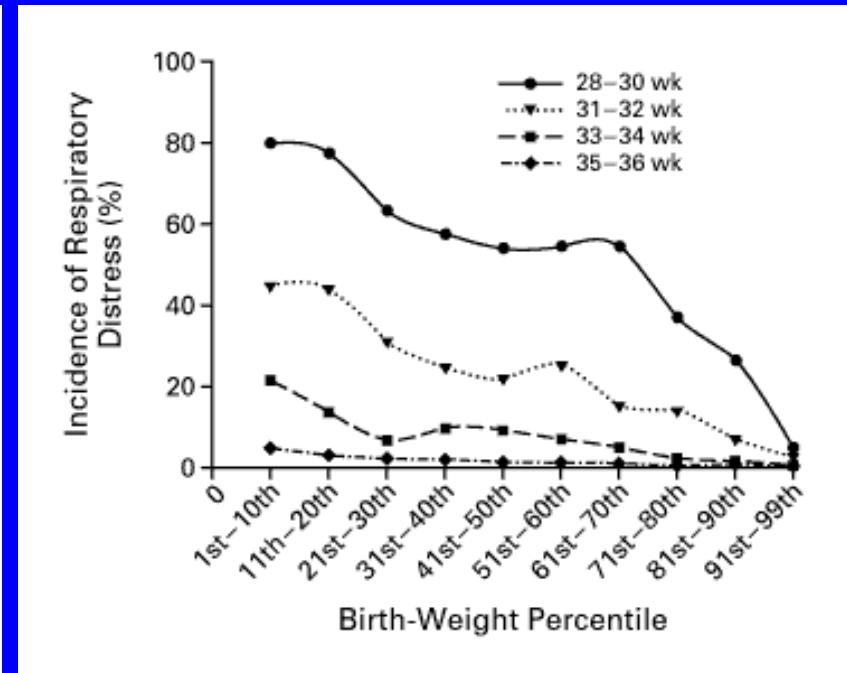


Figure 2. Incidence of Respiratory Distress among 12,317 Preterm Infants, According to Birth-Weight Percentile after Stratification according to Gestational Age (28 through 30 Weeks, 31 or 32 Weeks, 33 or 34 Weeks, and 35 or 36 Weeks).

Does LBW affect long-term health in adulthood? (Life-course effects)

- **Barker hypothesis** (*Am J Clin Nutr* 2000;71:1344S)
 - Fetal nutrition determines fetal growth and birth weight
 - Impaired fetal nutrition reflected by LBW can increase the risks of adult morbidity due to cardiovascular disease, toxemia, chronic obstructive pulmonary disease.
 - Is this impaired intrauterine growth or some common genetic mechanism (e.g. fetal insulin hypothesis)?
 - Need birth weight or SGA from early records

Mortality from Ischemic Heart Disease, by quartiles of Birth Weight for Gestational Age. Singleton Live Male Births 1915-29 Uppsala Academic Hospital

Fourth (No of Deaths) Birth Weight for Gestational Age	Adjusted Rate Ratio (95% CI)
1 st (n=203)	1.0
2 nd (n=173)	0.80 (0.62-1.04)
3 rd (n=127)	0.61 (*0.43-0.86)
4 th (n=144)	0.67 (0.43-1.02)
p-value for trend	0.003

Source: Leon DA. BMJ 1998; 317:241-5.

Hypertension During Pregnancy by Maternal Birth Status

Maternal Birth Status	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
SGA	1.7 (1.1-2.6)	1.8 (1.1-2.8)
Not SGA	1.0	1.0
Preterm	1.3 (0.8-2.0)	1.5 (0.96-2.5)
Not preterm	1.0	1.0

Klebanoff MA, Maternal size at birth and the development of hypertension during pregnancy. A test of the Barker Hypothesis. *Arch Intern Med* 1999; 159:1607-1612.

Genetic and familial factors affecting birth weight and gestational age

- Possible genetic characteristics of fetus or maternal genetic factors may affect fetal growth
 - Studies in twins and offspring of twins suggest ~ 40-50% of birth weight variability due to fetal genes (Magnus Clin Genet 1984;25:15)
 - Studies of familial correlations estimate genetic factors account for 31% of birth weight and 11% of gestational age variation (Lunde Am J Epidemiol 2007;165:734)
 - Genetic studies have linked genes on chromosome 6q to fetal growth (Arya Hum Mol Genet 2006;15:1569) and polymorphisms to SGA and pre-eclampsia in black women (Wang Am J Hum Genet 2006;78:770)

Infant Birth Weight and Gestational Age by Maternal Birth Weight

Mother's birth weight (lb)

Infant	2-3.9 (n=24)	4-5.9 (n=173)	6-7.9 (n=751)	≥8 (n=400)	p ^a
Mean Birth Weight, g	3,204	3,091	3,267	3,415	<0.001
No (%) LBW	0 (0)	18 (10)	39 (5)	11 (3)	0.001
Mean length of gestation	39.7	39.8	39.9	40.0	0.77
No (%) PTD	2 (8)	8 (5)	44 (6)	14 (4)	0.30

a – F test for comparison of means, χ^2 test for comparison of percentages

Klebanoff MA. *JAMA* 1984; 252:2423-27.

Maternal Birth Weight Effects on Infant birth weight (Intergenerational)

- A mother's own birth weight predicts her infant's birth weight
- For every 100 g increase in maternal BW, infant BW increases 10-20 g
- Equivocal evidence of intergenerational effect on preterm delivery

Risk of Poor Pregnancy Outcomes by Maternal Pregnancy Outcome

Maternal status	Odds Ratio (OR) of poor pregnancy outcome among infants	
	SGA	PTD
SGA	2.21 (1.41, 3.48)	1.21 (0.62, 2.38)
PTD	2.96 (1.47, 5.94)	0.65 (0.15, 2.74)

Race/Ethnicity as Determinants of Poor Pregnancy Outcomes

- In the U.S., black infant mortality is twice that of white infants
- Higher LBW rates among blacks are primarily the result of higher preterm delivery rates
 - Black women experience twice the rate of preterm delivery of white women and these differences are greatest for the most vulnerable newborns (< 1500 gms or < 32 weeks)
- Higher rates of IUGR among black infants also contribute to the higher rates of LBW

Race/Ethnicity and Poor Pregnancy Outcomes

- Genetic selection? (teleologic argument that smaller babies confer protection from obstructed labor, “small is beautiful”)
- Poorer pre-pregnancy health of minority populations
 - Higher rates of infection? (Higher prevalence of GTIs, especially BV in African American women)
 - Higher rates of obesity and chronic disease

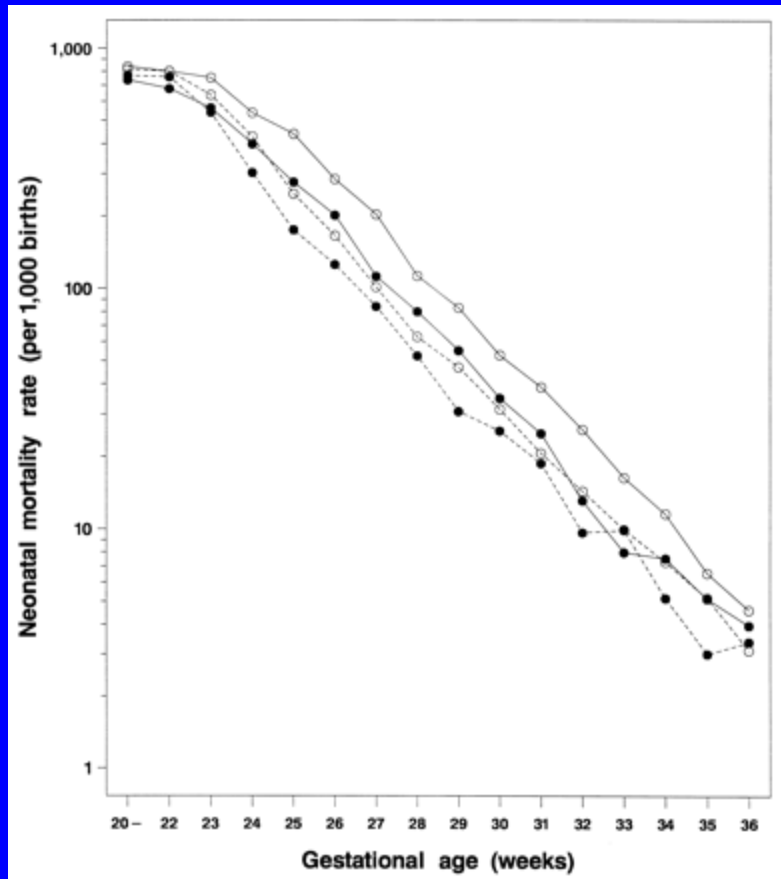
Racial Differences in LBW: African-American vs. African-born Blacks

- U.S.-born black women
 - LBW = 13.2%
- African-born black women (resident in US)
 - LBW = 7.2%
- White women
 - LBW = 4.3%
 - Cannot be due to “race” alone
 - David and Collins NEJM 1997;337:1209

Race/Ethnicity and Poor Pregnancy Outcomes

- Adjustment for traditional risk factors has failed to account for observed racial/ethnic differences
- Why?
 - Education level may not represent the same quality of life and opportunities for success for blacks and whites
 - Blacks and whites with college educations do not achieve similar levels of wealth

Racial differentials in neonatal mortality by gestational age in US born babies (1989-1997)



Neonatal mortality, by gestational age, for Black (•) and for White (o) infants in the United States. Solid lines denote data for 1989; dashed lines are for 1997. Data shown are for <37 weeks of gestation only.

Figure 1. Demissie K, et al. Trends in preterm birth and neonatal mortality among blacks and whites in the United States from 1989 to 1997. American Journal of Epidemiology Vol. 154, No. 4 : 307-315. All Rights Reserved.

Parental Race and LBW

- Black mother/black father LBW = 11.7
- Black mother/white father LBW = 8.3
 - Adj RR = 0.78 (0.68-0.73)
- White mother/white father LBW = 4.9
- White mother/black father LBW = 6.4
 - Adj RR = 1.05 (1.03-1.08)
- Cannot differentiate race from SES

• Parker *Epidemiol* 2000;11:242

Race and recurrence of PTD

(Kitska Am J Ob Gynecol 2007;196:131)

- Cohort of 2 or more singleton births between 1989-97
- 368,633 singleton deliveries , 63223 black
- Looked at risk of recurrence and timing of recurrent PTDs, adjusting for sociodemographic and health

Risks of Black/white PTD

PTD 20-34 weeks	OR black/white
Isolated PTD	2.41 (2.31-2.51)
Recurrent PTD crude	6.53 (6.14-6.94)
Recurrent PTD adjusted	4.11 (3.78-4.47)

Rates and risks of PTD 20-34 weeks by outcome of prior pregnancy and race

Risk of subsequent preterm birth in Missouri to a mother with either an initial preterm or full-term birth, according to race, 1989-1997.

	Initial preterm	Initial full-term	OR	CI (95%)
All births	12.34	3.59	3.78	3.66-3.91
Black	21.50	8.51	3.68	3.53-3.85
White	9.18	2.49	2.53	2.40-2.66

Race/Ethnicity and Poor Pregnancy Outcomes

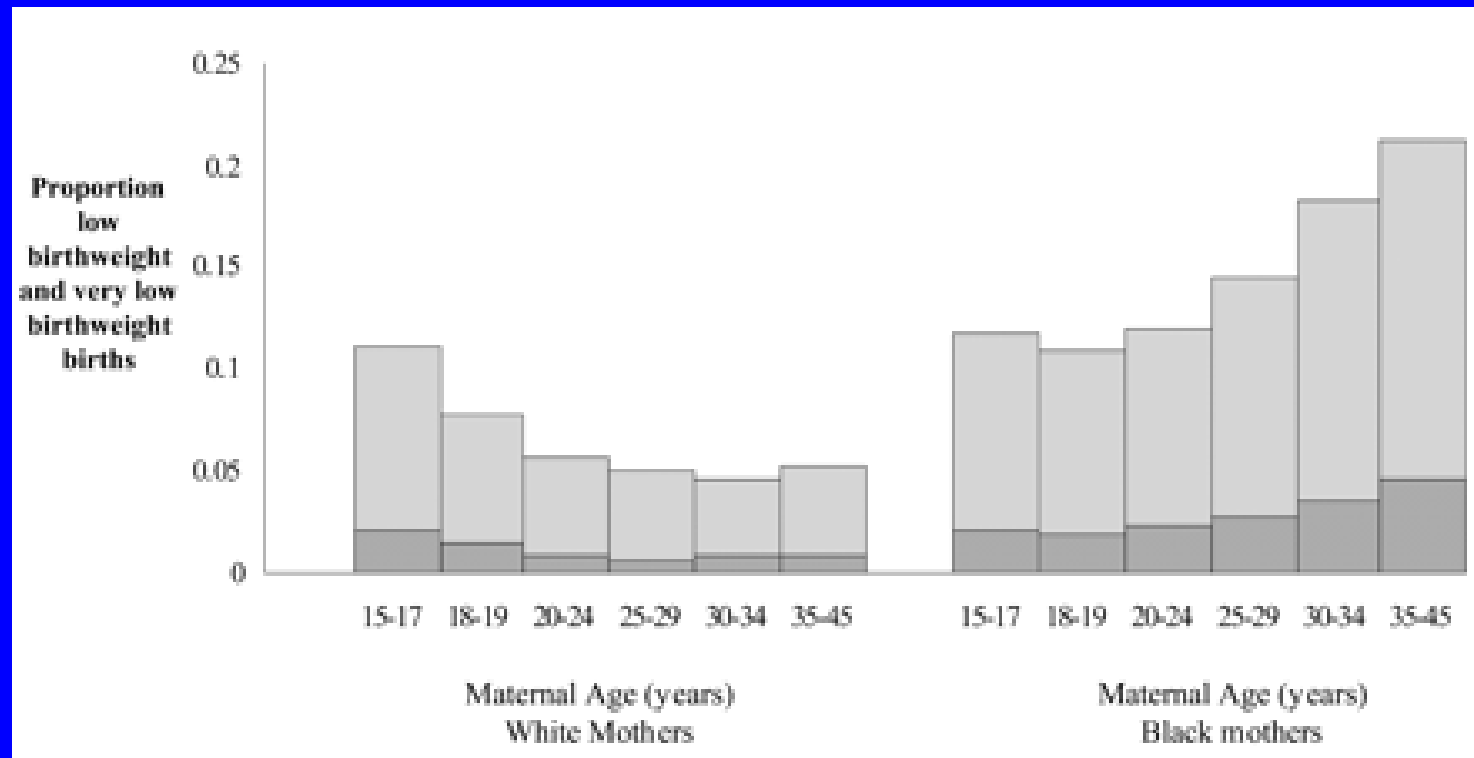
- Some traditional risk factors have been operationalized in a simplistic fashion
- Look beyond traditional factors
 - Psychosocial factors and physical activity
 - Home/neighborhood or work environment may help explain the race “gap” in pregnancy outcomes

Race/Ethnicity

Measurement of race and ethnicity is fraught with problems

- Frequently interpreted as a biological characteristic when it is a socially determined characteristic
- Definition of “race” problematic (self-reported on birth certificates, misclassification, mixed race)
- However, self-reported ethnicity reflects geographic ancestry when evaluated by genetic markers, and gene frequencies vary between geographic isolates

Maternal Age and LBW by Race



Proportion of low birthweight (<2500 g) and very low birthweight (<1500 g) births by maternal age and ethnicity

Rich-Edwards JW et al. Diverging associations of maternal age with low birthweight for black and white mothers. *Int J Epidemiol* 2003;32:83-90. All Rights Reserved.

LBW by Maternal Age, Race and Poverty

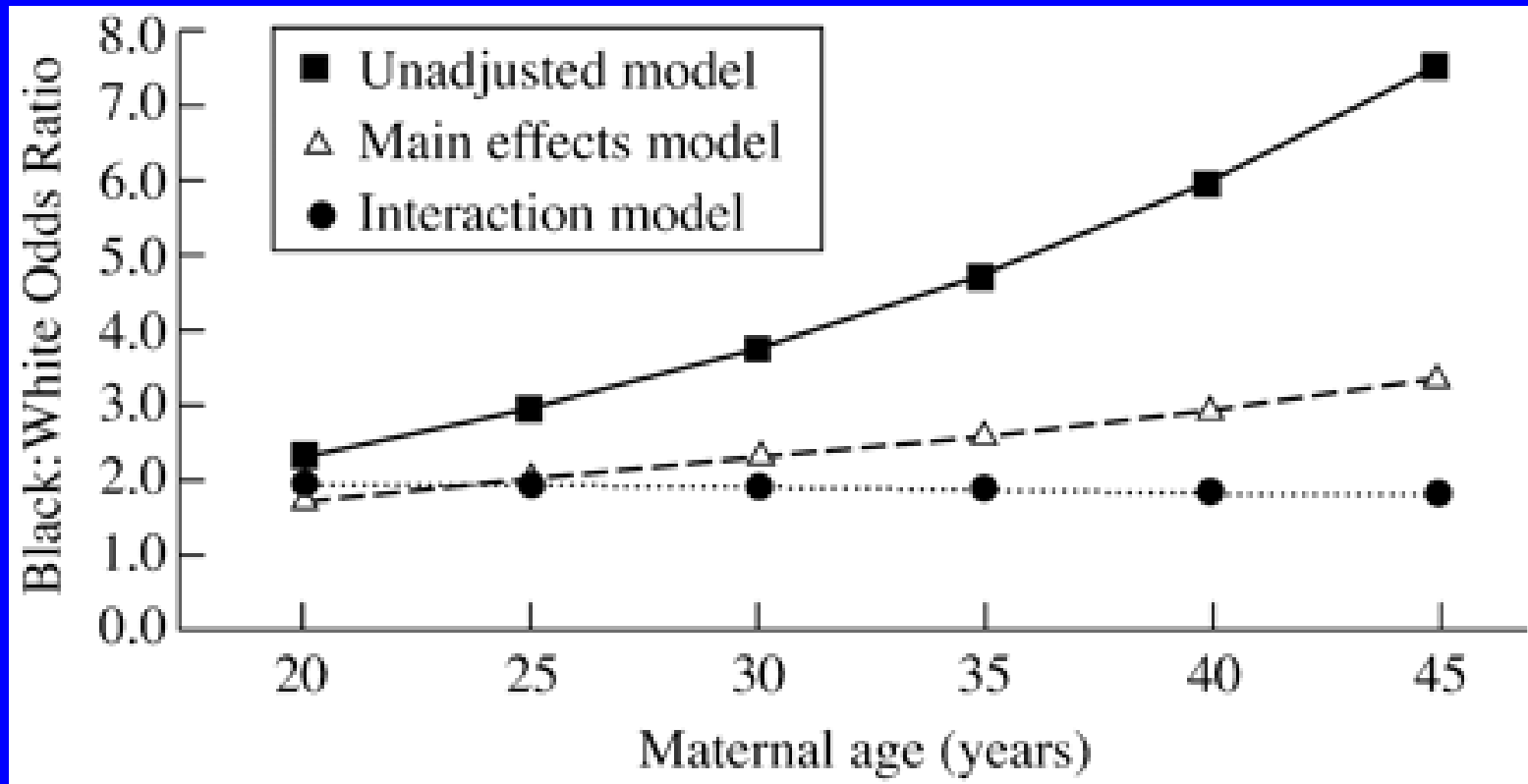
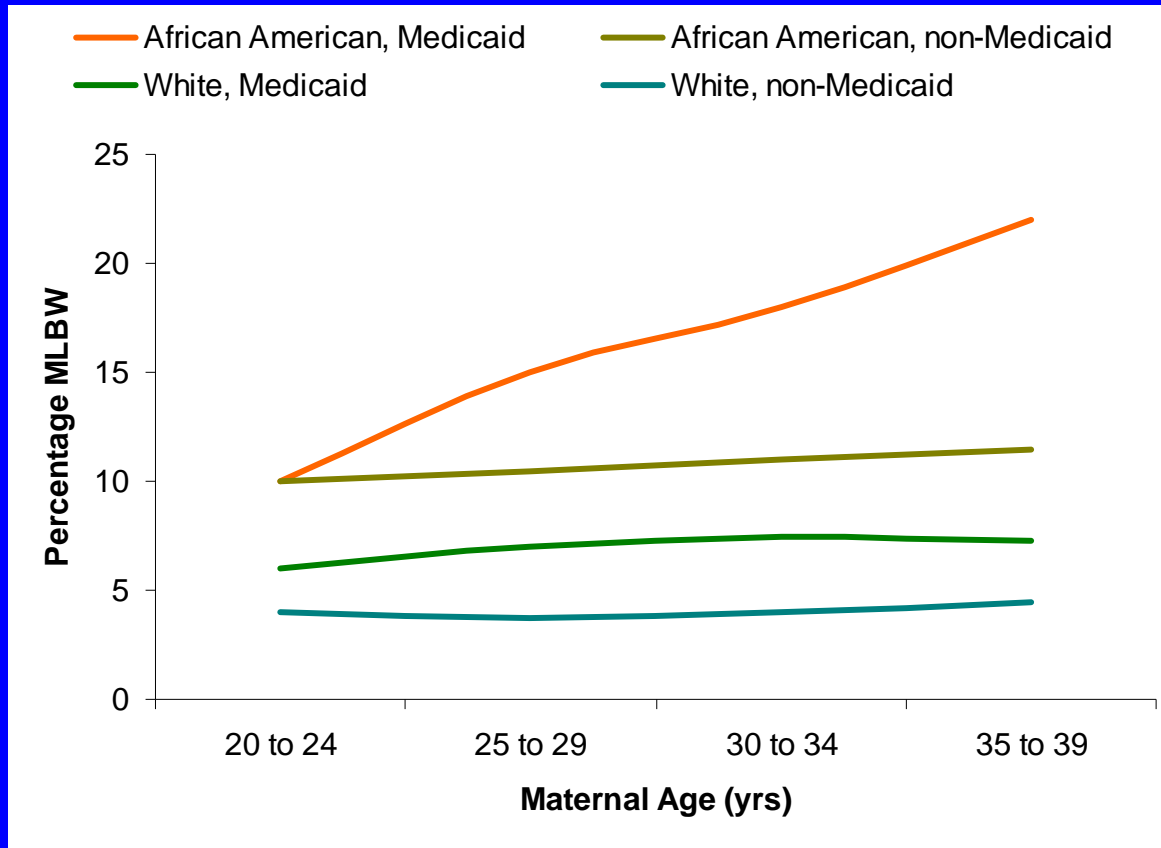


Figure 2 Odds ratios of delivering low birthweight for black mothers compared with white mothers by maternal age, derived from three models. Chicago, 1994–1996

Rich-Edwards JW et al. Diverging associations of maternal age with low birthweight for black and white mothers. *Int J Epidemiol* 2003;32:83-90. All Rights Reserved.

LBW by Maternal Age, Race and Poverty



Black mothers
Have higher LBW
At all ages and level
Of poverty

Maternal Age and Preterm Delivery

- Younger age at first birth associated with increased PTD. Is it immaturity or social effect?
- Older age also associated with PTD

Age	PTD (%)
< 20	11.5
20-24	6.3
25-34	5.2
35+	9.0

Adolescent Pregnancy and PTD

- Younger adolescents have increased risk of PTD and Very Preterm Delivery (VPTD)

Age	33-36 wks (%)	≤32 wks (%)
13-15	9.0	5.9
16-17	7.3	2.5
18-19	5.9	1.7
20-24	4.5	1.1

Parity and Pregnancy Outcomes

- Low and high parity associated with both LBW and PTD

Parity	LBW (%)	PTD (%)
0	7.6	4.7
1	5.4	3.9
2-3	6.8	5.2
4+	7.4	5.5

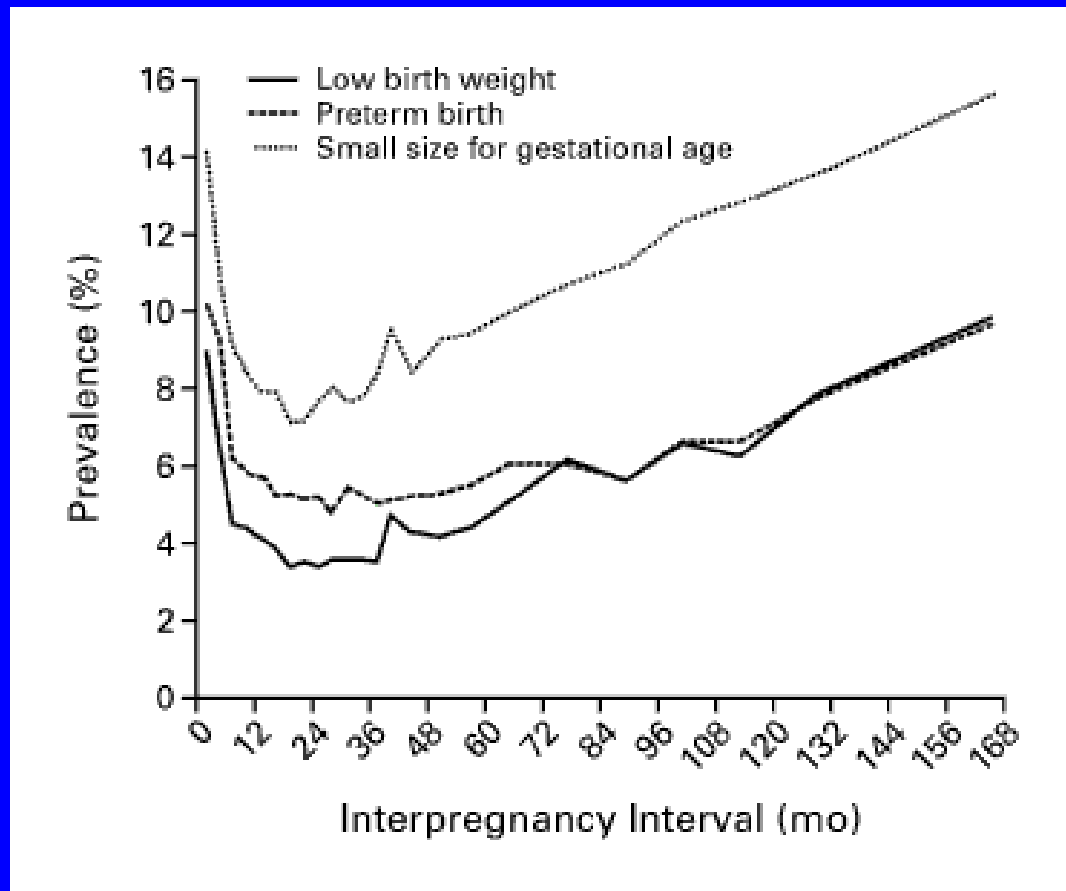
Age, Parity and Pregnancy Outcomes

- Maternal age may be associated with other factors independently associated with increased risk of poor pregnancy outcomes
 - First pregnancy in older mothers may explain increased risk rather than age *per se*
 - Older mothers may have more chronic medical problems
 - Young motherhood also associated with lower SES, nutritional inadequacy, lower prepregnancy weight and pregnancy weight gain, and higher stress

Birth Spacing and Poor Pregnancy Outcomes

- Do short intervals between subsequent pregnancies lead to impaired fetal nutrition and higher risk of LBW, PTD, SGA?
- Is there an optimal interval between births?

Prevalence of Adverse Perinatal Outcomes According to Interpregnancy Interval. 173,205 Singleton Infants



Source: Zhu BP, Rolfs RT, Nangle BE, Hopan JM. Effect of the interval between pregnancies on perinatal outcomes. *NEJM* 1999;340:589-94. Copyright © 1999. Massachusetts Medical Society. All Rights Reserved.

Short (≤ 12 months) Interpregnancy Intervals and Low Birth Weight by ethnicity

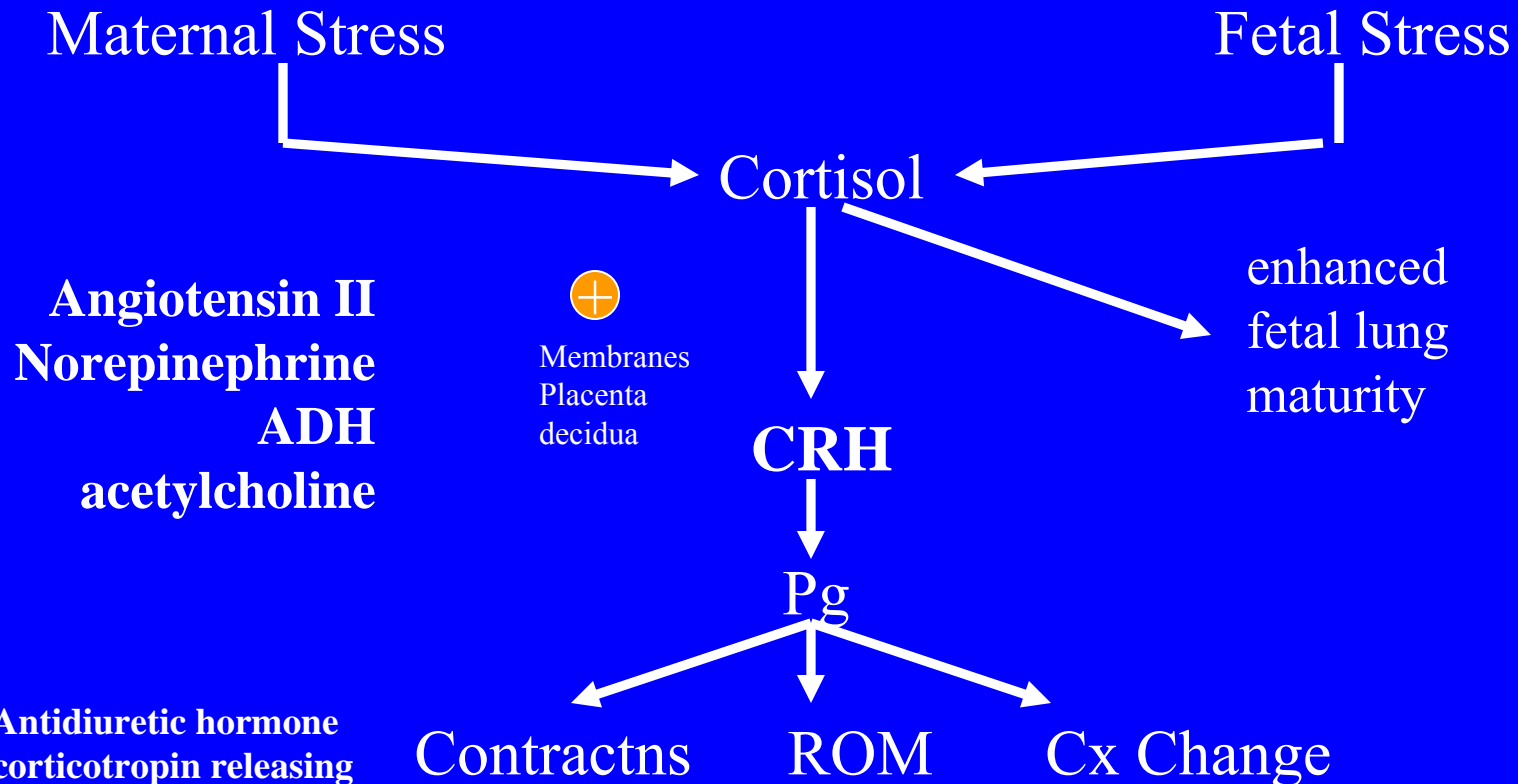
	Low Birth Weight (<2.5 kg)			
	Interval: < 6 months		Interval: 6-12 months	
	OR	95% CI	OR	95% CI
African Americans	1.34	1.30-1.37	0.98	0.96-1.00
Mexicans	1.38	1.32-1.44	0.98	0.94-1.02
Native Americans	1.07	0.91-1.26	0.92	0.79-1.07
Non-Hispanic Whites	1.28	1.26-1.31	0.98	0.96-1.00
Puerto Ricans	1.28	1.13-1.44	1.02	0.90-1.15

Khoshnood B. et al. *Am J Epidemiol* 1998; 148:798-805.

Stress and Pregnancy

- Physiology
- Physical stressors
- Psychogenic stress
- Evidence of associations with PTD, PROM
- Some evidence of association with LBW, IUGR

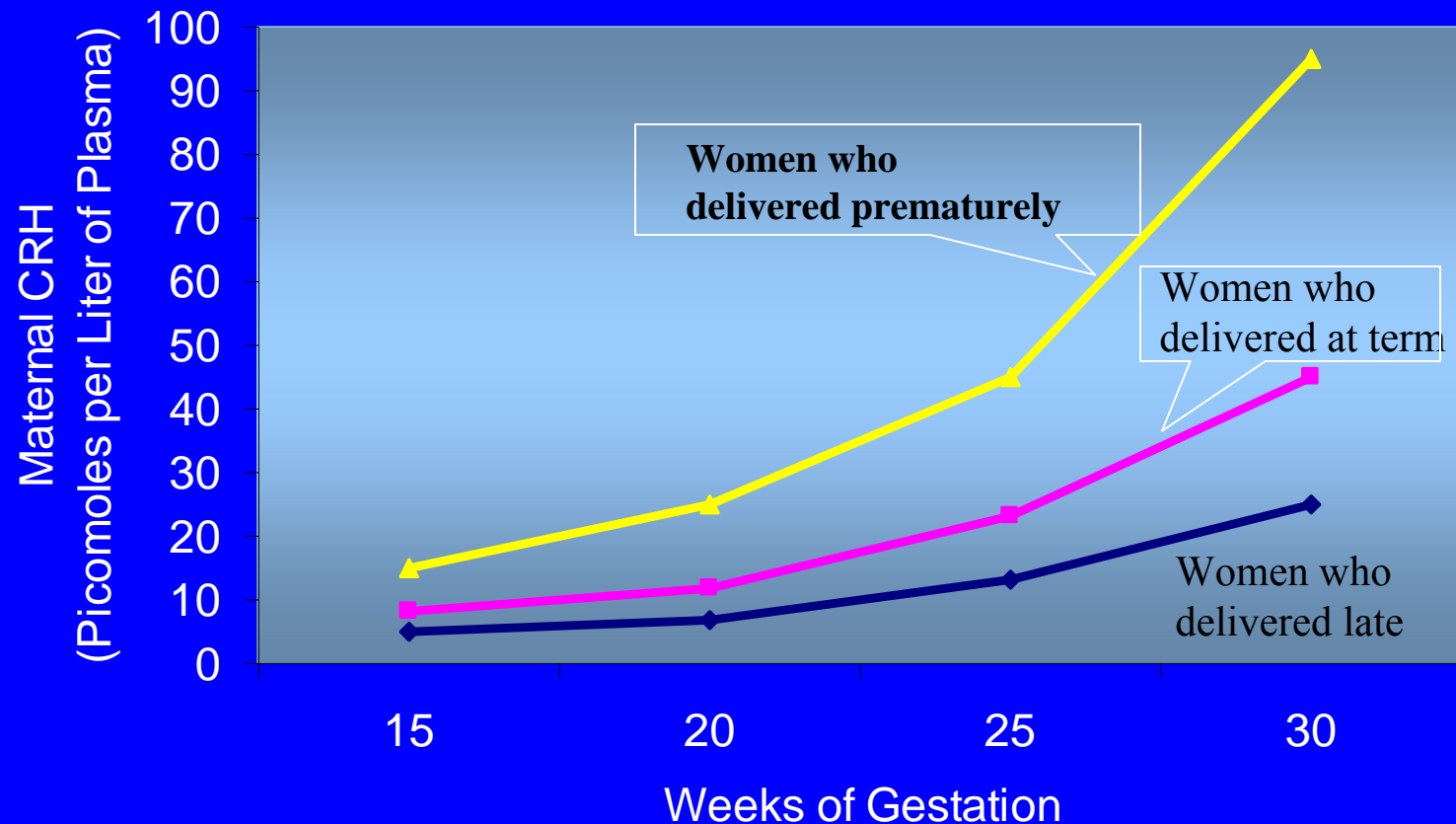
Pathway for Action of Placental Corticotropin Releasing Hormone on Parturition



ADH – Antidiuretic hormone
 CRH – corticotropin releasing hormone
 Pg - prostaglandin
 Ctx - contractions
 ROM – rupture of membranes
 Cx - cervix

Lockwood CJ. Am J Obstet Gynecol 1999; 180:S264-6.

Maternal CRH by Week of Gestation



Smith R. Scientific American 1999; March:68.

Physical Stressors

- Infection
- Physical
 - Heat, noise exposures at work
 - Standing on the job
 - Heavy lifting
 - violence
- Nutritional

Physical Stress

- **Physical stress in the workplace**

PTD risk among prospective cohort of working Danish women (Henriksen, Br J Obstet Gynaecol, 1995):

- >5 hours standing and walking OR for PTD=3.3 (1.4, 8.0)

- **Physical activity**

PTD risk among cohort of low-income urban women in U.S. (Misra, Am J Epidemiol, 1998)

- Increased risk for physical activities of daily living
 - Climbed stairs ≥ 10 x/day, PTD OR = 1.60 (1.05, 2.46)
- Decreased risk for leisure-time exercise,
 - Exercise ≥ 60 x in 1st-2nd trimester, PTD OR = 0.51 (0.27, 0.95)

Psychosocial Stress

- Psychosocial measures
 - Life events
 - Job demands vs. control
 - Time pressures
 - Interpersonal relationships/social support
- Chronic vs. Acute
- Timing in pregnancy

Measurement of Acute Antenatal Stress

- Life events scales
 - Nature of event (e.g. job loss, marital disruption)
 - Timing, # events
 - Objective assessment of events
- Perceptions, subjectivity of response to life events (Lazarus)
 - **Stressors** are the sources of stress (can be quantified)
 - **Stress** is the perceived experience and may vary with personality type, social setting etc. (Hard to quantify)
 - Social support

Stress measurement

- Likert scales for psychosocial domains (Assessment of Psychosocial Status in Pregnancy, NICHD)
 - Anxiety
 - Self-esteem
 - Mastery
 - Depression
 - Stress

Measurement of Antenatal Stress: Recall Bias

- Subjective nature of information
- Information obtained after completed pregnancy biased by anxiety (e.g., having a PTD)
- Need measurements during pregnancy prior to outcome

Prospective study of stress and PTSD

- 1962 women assessed during pregnancy
- **Risks of PTSD**
 - High pregnancy related anxiety RR = 1.4 (1.0-2.0)
 - Negative life events RR = 1.8 (1.2-2.7)
 - Perceived racial discrimination RR = 1.4 (1.0-2.0)

(Dole Amer J Epidemiol 2003; 157:14)

Stress and LBW/IUGR

- **Exposure to stressors and race**

Low income cohort in Baltimore - (Orr, Am J Prev Med, 1996): LBW risk among women exposed to moderate/high stressors

- African-American women, OR=1.52 (1.33, 1.91)
- Caucasian women, OR=0.48 (0.01, 1.37)

- **Psychosocial resources**

Prospective cohort in Sweden – SGA risk (Dejin-Karlsson, BJOG, 2000)

- Poor social network index, OR = 3.3 (1.6, 6.7)
- Poor social support index, OR = 2.7 (1.3, 5.6)

Acute Stress and Modifiers of Response I

- **Personality and cognitive response**
 - Sweden at time of Chernobyl: Women with high psychic and somatic anxiety scores had shorter gestation, but women with low scores had no effect (Levi *J Psychosom Obstet Gynecol* 1989;10:221)
 - Positive correlation between PTSD and “psychopathologic score” (negative attitudes towards pregnancy) (Mamelle *AJE* 1989;130:989)

Acute Stress and Modifiers of Response

- **Social Support**

- Some observational studies suggest social support can mitigate effects of life events
- Randomized trial of improved social support showed no benefit (Spencer *Br J Obstet Gynecol* 1989;96:281)

- **Nutritional status**

- Poor psychosocial profile increased risk of IUGR among low-income, minority U.S. women who were thin
- Poor psychosocial profile:
 - Women with BMI < median, RR=2.11 (1.47, 3.04)
 - Women with BMI ≥ median, RR=1.20 (0.73, 1.98)(Cliver, *Obstet Gynecol* 1992;80:262)

Measurement of Chronic Antenatal Stress

- Chronic Stressors/Stress
 - Poverty
 - Racism
 - Family (spouse, children)

Biomarkers

- Measure hormonal response to stress to avoid subjectivity and to capture cognitive response
 - Noradrenaline
 - Salivary alpha amylase
 - CrH
 - Associations between biochemical markers and increased risk of PTD and LBW
 - Problem elevation of biomarkers occurs late in pregnancy and cannot be used for prevention

Corticotropin-Releasing Hormone and Parturition

Reference	Study population	Key CRH findings	
		Study pop'n	Normal
Warren et al. 1992	Preterm labor (PTL)	1240 ± 320	600 ± 67
Ruth et al. 1993	Preeclampsia PROM	24.1 (14.2-67) 17.0 (7.65-53)	6.35 (1.0-27.5)
Tropper et al. 1992	Preeclampsia, PROM, PTL	1058 ± 184	456 ± 71