

Understanding Prematurity and its Relation to Birth Defects



Sonja A Rasmussen, MD, MS

*Division of Birth Defects and Developmental Disabilities,
National Center on Birth Defects and Developmental
Disabilities, CDC, Atlanta, GA*



• *The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.*



Overview

- **Prematurity and birth defects account for more than half of all infant deaths**
- **Preterm infants have a higher rate of birth defects**
- **Prematurity has important implications for birth defects surveillance**

Definitions

- **Preterm (premature) – Live born infant delivered before 37 completed weeks gestational age**
- **Low birth weight – Live born infant weighing less than 2,500 grams (5 lbs., 8 oz.) at birth**

Relationship between Preterm and Low Birth Weight

- **Preterm (premature)**
 - Birth weight can be low (< 2,500 grams) or not
- **Low birth weight**
 - Infant can be preterm (< 37 weeks) or not: (small for gestational age [SGA], also called intrauterine growth retardation [IUGR])

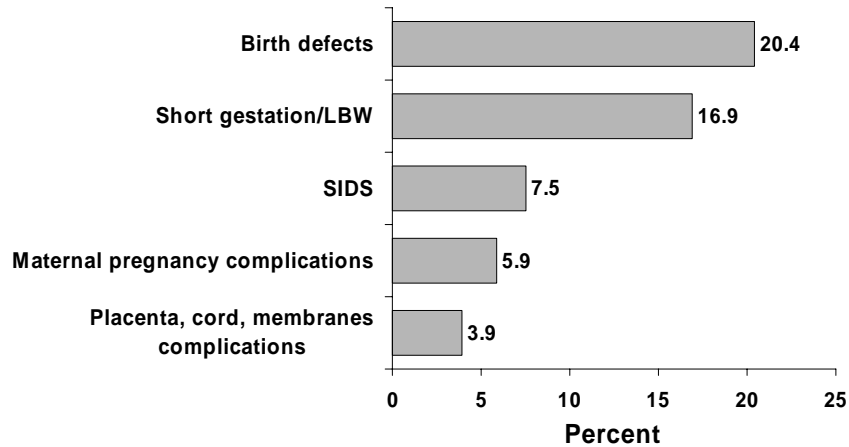
**Prematurity and birth defects
account for more than half of
all infant deaths**

US Infant Mortality

- **US infant mortality rate is higher than most other developed countries**
 - As of 2004, US ranked 29th in the world in infant mortality, tied with Poland and Slovakia
- **Gap between US and countries with the lowest infant mortality rates appears to be widening**
- **Much of the lack of decline in US infant mortality appears to be related to increases in preterm birth and its associated mortality**

<http://www.cdc.gov/nchs/data/databriefs/db09.htm#howdoes>

Leading Causes of Infant Mortality, United States, 2006



Heron et al., Natl Vital Stat Reports. 56(16) – Released June 11, 2008

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Contribution of Preterm Birth to Infant Mortality Rates in the United States

William M. Callaghan, MD, MPH^a, Marian F. MacDorman, PhD^b, Sonja A. Rasmussen, MD, MS^c, Cheng Qin, MD, DrPH^a, Eve M. Lackritz, MD^a

^aDivision of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; ^bDivision of Vital Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland; ^cDivision of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

Callaghan et al., Pediatrics 118:1566-1573, 2006

Preterm Birth and Infant Mortality: Analysis

- **Identified top 20 leading causes of infant death in 2002 in the US**
- **Assessed role of preterm birth for each cause**
 - **Proportion of infants who were born preterm ($\geq 75\%$)**
 - **Cause considered to be direct consequence of preterm birth, based on clinical evaluation and review of literature**

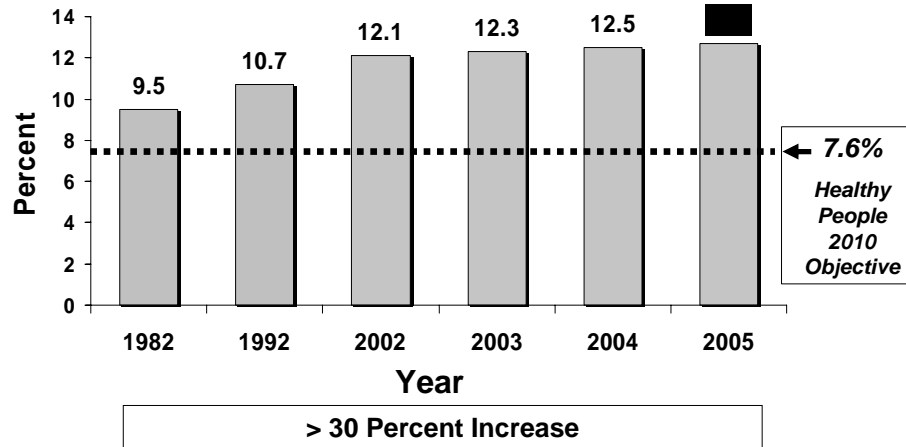
Callaghan et al., Pediatrics 118:1566-1573, 2006

Preterm Birth and Infant Mortality: Results

- **9,596 infant deaths were attributable to preterm birth (34.3% of all infant deaths)**
- **95% of these were born at < 32 weeks gestation and weighed < 1500 g**
- **68.8% died in the first 24 hours of life**
- ***Over half (54.5%) of infant deaths are related to preterm birth or birth defects***

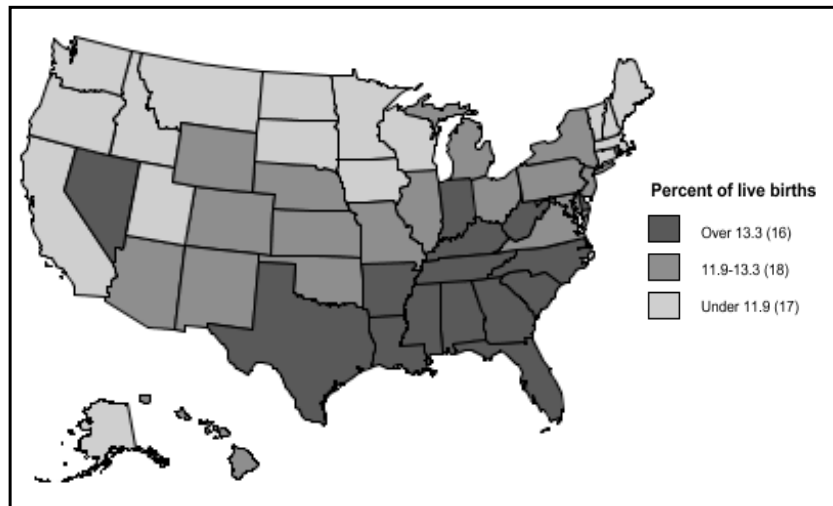
Callaghan et al., Pediatrics 118:1566-1573, 2006

Preterm Births, United States, 1982-2005



National Center for Health Statistics, final natality data (1982-2005)

Preterm Birth Rates by State United States, 2005



Source: National Center for Health Statistics, final natality data
Retrieved July 29, 2008, from www.marchofdimes.com/peristats



Preterm infants have a higher rate of birth defects

Risk for birth defects among premature infants: A population-based study

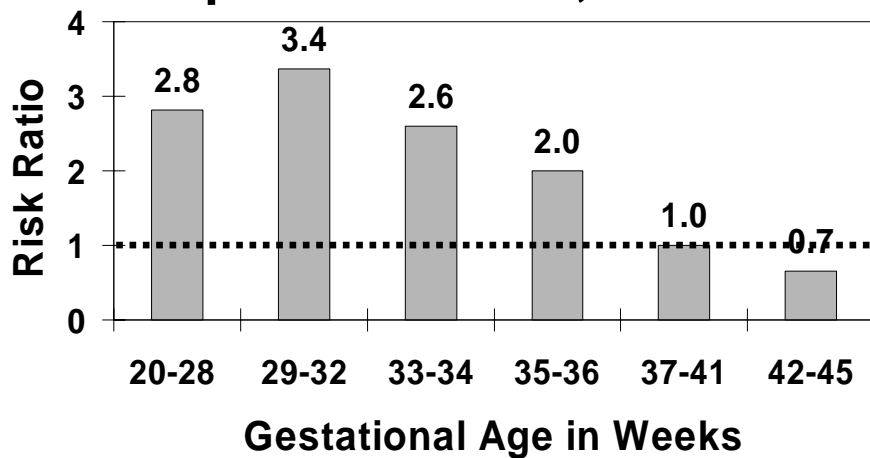
*Sonja A. Rasmussen, MD, MS, Cynthia A. Moore, MD, PhD, Leonard J. Paulozzi, MD, MPH, and
Elaine P. Rhodenbiser*

Rasmussen et al., J Pediatr 138:668-73, 2001

Methods

- Population-based cohort study
- Study population
 - ~265,000 live born singleton infants born in the five-county metropolitan Atlanta area from 1989-1995
 - Data on 7,738 babies with birth defects from Metropolitan Atlanta Congenital Defects Program (MACDP)
 - Preterm infants (< 37 weeks gestation) with isolated prematurity-related defects excluded from affected group

Relationship between Gestational Age and Risk for Birth Defects, Metropolitan Atlanta, 1989-1995



Rasmussen et al., J Pediatr 138:668-73, 2001

Types of Birth Defects and Risk for Preterm Birth

<i>Type of Birth Defect</i>	<i>Risk Ratio (95% CI)</i>
Anencephaly	3.51 (0.97-11.0)
Spina bifida	3.04 (1.78-5.03)
Transposition great vessels	1.62 (0.95-2.63)
Cleft palate	2.41 (1.52-3.73)
Small intestinal atresia	10.37 (5.42-20.1)
Congenital hip dislocation	1.10 (0.72-1.64)
Gastroschisis	8.75 (5.24-14.6)
Down syndrome	3.03 (2.29-3.99)

Rasmussen et al., J Pediatr 138:668-73, 2001

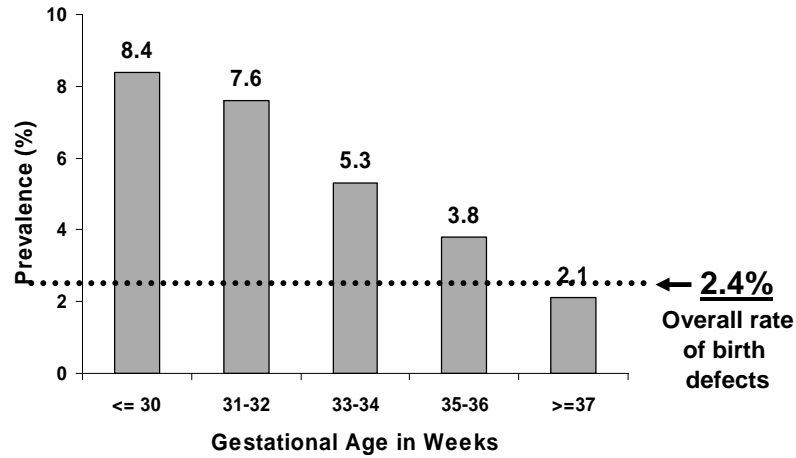
Role of structural birth defects in preterm delivery

Gary M. Shaw^a, David A. Savitz^b, Verne Nelson^a and John M. Thorp Jr^c

^aMarch of Dimes Birth Defects Foundation, California Birth Defects Monitoring Program, Oakland, CA, ^bDepartment of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, ^cCecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

© Blackwell Science Ltd. *Paediatric and Perinatal Epidemiology* 2001, 15, 106-109

Prevalence of Birth Defects in Infants and Fetuses, by Gestational Age, California, 1984-1996



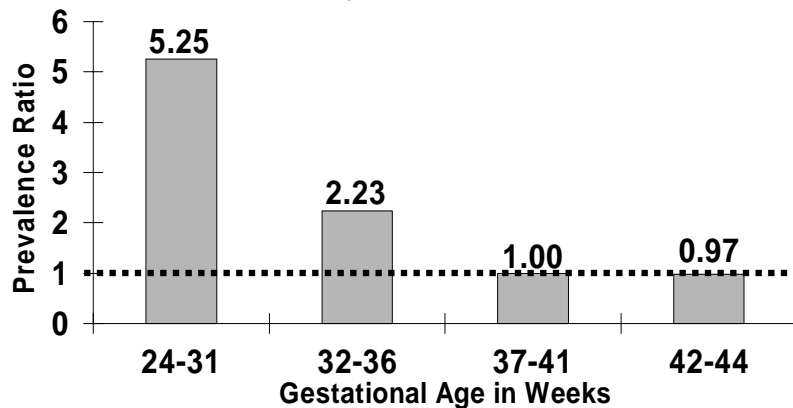
Shaw et al., *Paediatr Perinatal Epidemiol* 15:106-109, 2001

Matern Child Health J
DOI 10.1007/s10995-008-0348-y

The Association Between Major Birth Defects and Preterm Birth

Margaret A. Honein · Russell S. Kirby · Robert E. Meyer · Jian Xing ·
Nyasha I. Skerrette · Nataliya Yuskiv · Lisa Marengo · Joann R. Petrini ·
Michael J. Davidoff · Cara T. Mai · Charlotte M. Druschel · Samara Viner-Brown ·
Lowell E. Sever · for the National Birth Defects Prevention Network

Relationship between Gestational Age and Risk for Birth Defects, 13 states*, 1995-2000**



* Data from CO, GA, HI, IL, KY, MI, MO, NY, NC, OK, RI, TX, WV

** Adjusted for state, maternal age, maternal race/ethnicity, and timing of prenatal care

Honein et al., Matern Child Health J 2008 May 17 [Epub ahead of print]

Possible Reasons for Association Between Prematurity and Birth Defects

- Prenatal diagnosis of birth defect may result in delivery at preterm gestational age
- Certain birth defects may increase probability of preterm labor
- Prematurity and birth defects may share common risk factors

Risk Factors for Preterm Labor/Delivery

- **The best predictors of having a preterm birth are**
 - **History of preterm labor/delivery**
 - **Multi-fetal gestation**

Other Risk Factors for Preterm Labor/Delivery

- **Maternal age (<17, >35 yrs)**
- **Black race**
- **Low socioeconomic status**
- **Unmarried**
- **Lack of social supports**
- **Major stress**
- **Uterine abnormalities**
- **Incompetent cervix**
- **Infections**
- **Folic acid deficiency**
- **Bleeding**
- **Anemia**
- **Low pre-pregnant weight**
- **Obesity**
- **Genetic predisposition**
- **Previous fetal/neonatal death**
- **3+ spontaneous losses**
- **Tobacco use**
- **Illicit drug use**
- **Alcohol abuse**

Implications for Birth Defects Surveillance

- **Recognition of this association may assist in birth defects surveillance**
- **Further study of this association may provide insight into the basic mechanisms of birth defects and preterm delivery**

Why is Prematurity Important for Birth Defects Surveillance?

- **Preterm infants have medical complications that are not birth defects**
- **Case definition for birth defects is for full-term infants**
 - **Some birth defects are developmentally normal for preterm infants**
- **Preterm infants have medical complications that may mimic birth defects**

**Preterm infants have
medical complications that
are not birth defects**

**Medical Complications of
Prematurity that are NOT
Birth Defects**

- **Infant respiratory distress syndrome**
- **Bronchopulmonary dysplasia**
- **Intraventricular hemorrhage**
- **Kernicterus**
- **Retinopathy of prematurity**
- **Necrotizing enterocolitis**

Infant Respiratory Distress Syndrome

- **Previously called hyaline membrane disease**
- **Most common cause of respiratory failure in first days of life**
- **Inadequate amounts of lung surfactant and immaturity of lungs result in collapse of alveoli and terminal bronchioles**
- **Over 30 years ago - ~50% of affected infants died, now 85-95% survive**

Implications for Birth Defects Surveillance

- **Birth defects surveillance staff members need to be familiar with prematurity-related complications**
- **Information on these complications should never be included as a birth defect in surveillance systems (although may be helpful for abstractors to document)**

**Some birth defects are
developmentally normal for
preterm infants**

**Some Birth Defects Developmentally
Normal for Preterm Infants**

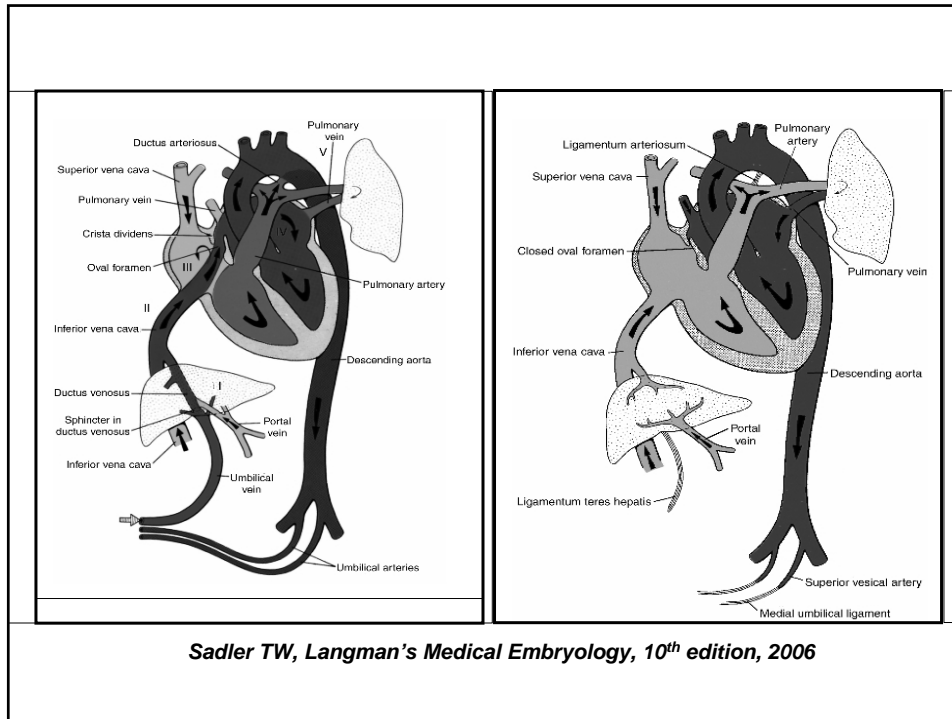
- **Structure necessary for
intrauterine survival**
- **Infant delivered or pregnancy
terminated before development
complete**

Developmentally Normal Conditions in the Preterm Infant

- Absent/decreased ear cartilage
- Blue sclera
- Large fontanelles
- Hypoplastic nipples
- Patent ductus arteriosus (PDA), patent foramen ovale (PFO)
- Hypoplastic lungs
- Prominent clitoris, hypoplastic labia majora
- Undescended testes
- Hypothyroidism
- Excess lanugo

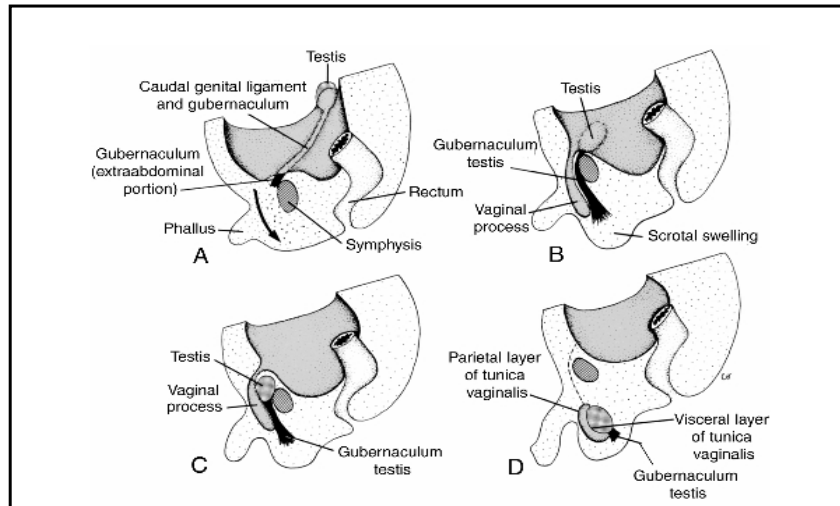
Closure of Ductus Arteriosus

- **Full-term infants**
 - Closure in 50% by 24 hours, 90% by 48 hours, all by 72 hours
- **Preterm infants**
 - 30-36 weeks – incidence of PDA beyond 4 days – 11%
 - < 30 weeks – incidence of PDA beyond 4 days – 65%



Undescended Testes (Cryptorchidism)

- **Timing of descent of testes**
 - By 28 weeks, testes have descended from posterior abdominal wall to deep inguinal rings
 - Descent through inguinal canals begins in 28th week, takes 2-3 days
 - By 32 weeks, testis enters scrotum
- **Undescended testes occurs in 3% of full-term males, 30% of premature males**



Sadler TW, Langman's Medical Embryology, 10th edition, 2006.

Implications for Birth Defects Surveillance

- Information on gestational age needs to be abstracted on infants with birth defects
- Instructions are available that specify how to handle these defects (conditional, special or excluded)

**Preterm infants have
medical complications that
may mimic birth defects**

**Medical Conditions in Preterm
Infants that Mimic Birth Defects**

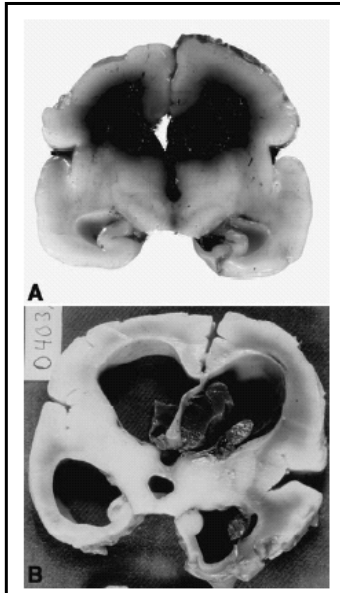
- Hypoxic-ischemic encephalopathy (cortical atrophy, microcephaly)
- Hydrocephalus secondary to intraventricular hemorrhage
- Strabismus, exotropia, esotropia
- Lung cysts secondary to BPD/assisted ventilation
- Subglottic stenosis secondary to intubation
- Head deformations (scaphocephaly, dolichocephaly, plagiocephaly)

Hydrocephalus secondary to Intraventricular Hemorrhage (IVH)

- **Up to 80% of infants born 23-24 weeks gestation develop IVH arising from periventricular germinal matrix (PGM)**
- **PGM established early in brain development – site of differentiation of neurons and glia, nearly disappears by 35-36 weeks**

Hydrocephalus secondary to Intraventricular Hemorrhage (IVH)

- **Hemorrhage may be confined to PGM or break into ventricle**
- **More extensive hemorrhages → interfere with circulation of cerebrospinal fluid → posthemorrhagic hydrocephalus**



**IVH in a preterm infant
who died at age 3 days**

**Post-hemorrhagic
hydrocephalus in a
preterm infant who died
at age 4 weeks**

Cherian et al., Brain Pathol 14:305-311, 2004

Implications for Birth Defects Surveillance

- **Some defects may be secondary to prematurity-related complications or treatment**
- **Age at onset and previous treatment need to be carefully noted**
- **If unclear whether defect should be coded or not, clinical reviewers can assist**

Summary

- Prematurity and birth defects account for more than half of all infant deaths
- Preterm infants have a higher rate of birth defects
- Prematurity has important implications for birth defects surveillance

Acknowledgments

- Cynthia Moore
- Siobhan Dolan
- Motoko Oinuma
- Jaime Frías

