

# Understanding Prematurity and its Relation to Birth Defects



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*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**

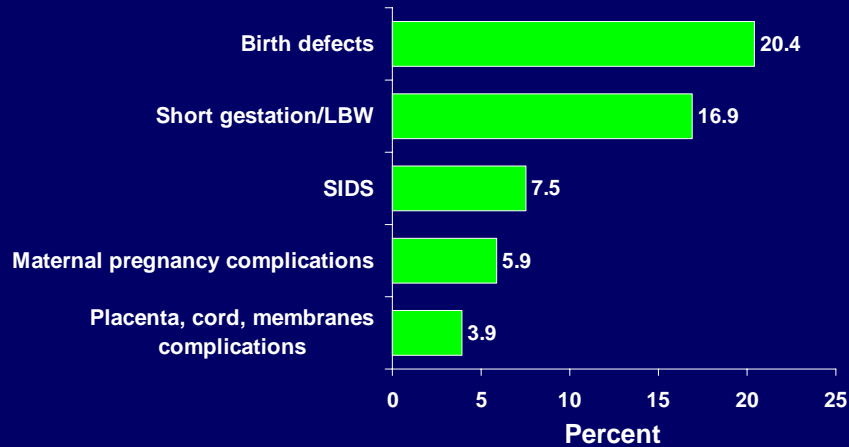
### **US Infant Mortality**

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- **US infant mortality rate is higher than most other developed countries**
  - As of 2004, US ranked 29<sup>th</sup> 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*

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

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

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*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

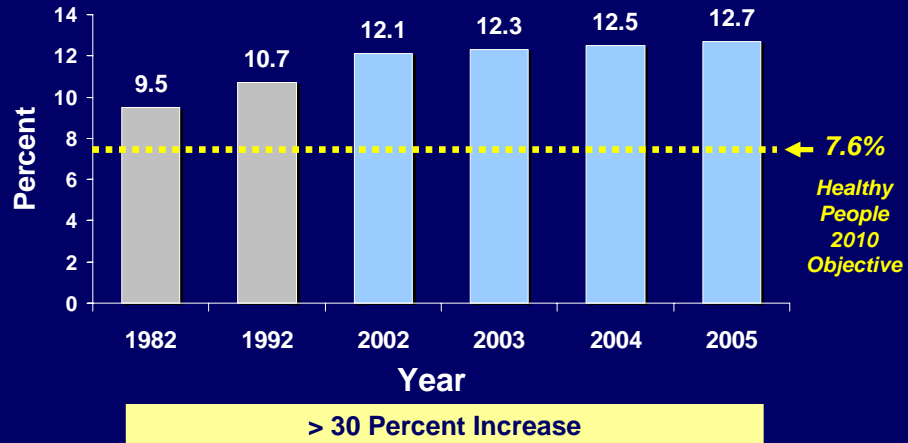
*Callaghan et al., Pediatrics 118:1566-1573, 2006*

## 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*

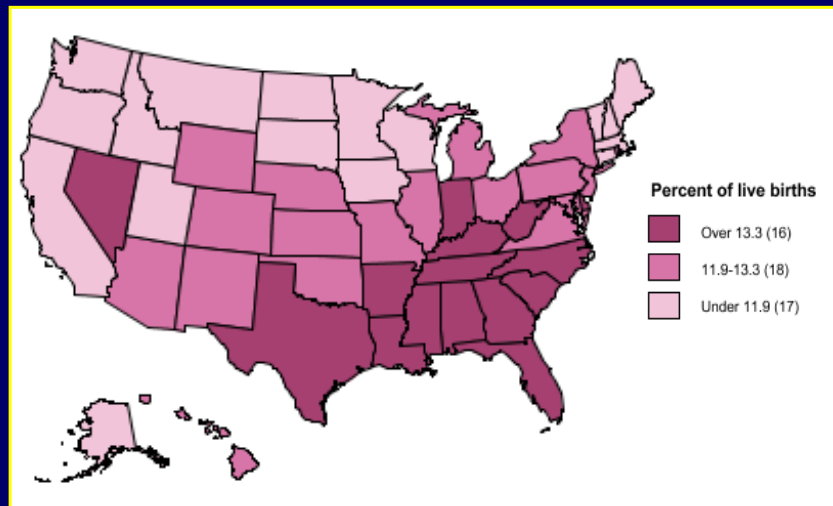
*Callaghan et al., Pediatrics 118:1566-1573, 2006*

## 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](http://www.marchofdimes.com/peristats)



## Preterm infants have a higher rate of birth defects

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

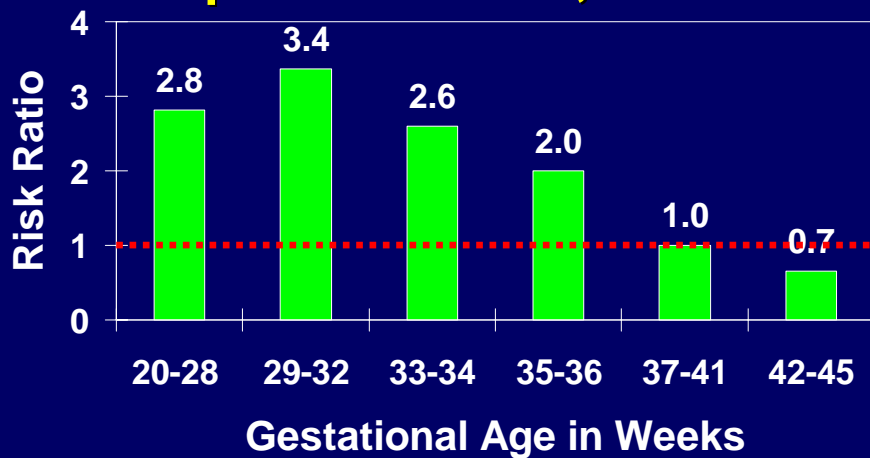
*Sonja A. Rasmussen, MD, MS, Cynthia A. Moore, MD, PhD, Leonard J. Paulozzi, MD, MPH, and Elaine P. Rhodenbiser*

*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*

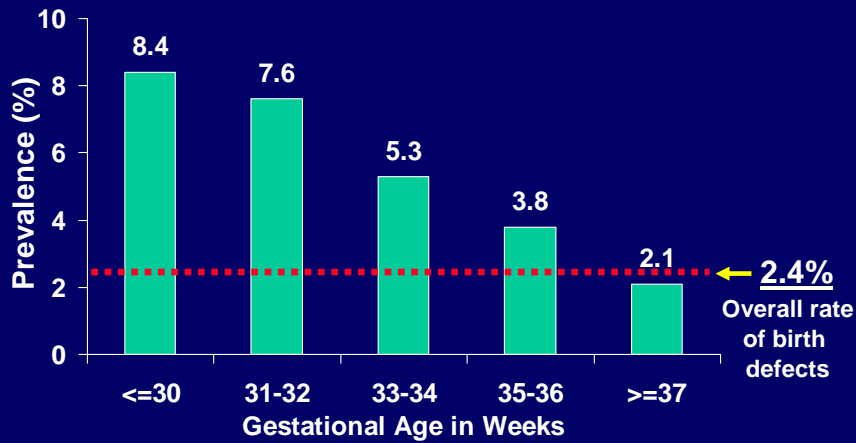
### Role of structural birth defects in preterm delivery

Gary M. Shaw<sup>a</sup>, David A. Savitz<sup>b</sup>, Verne Nelson<sup>a</sup> and John M. Thorp Jr<sup>c</sup>

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© 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



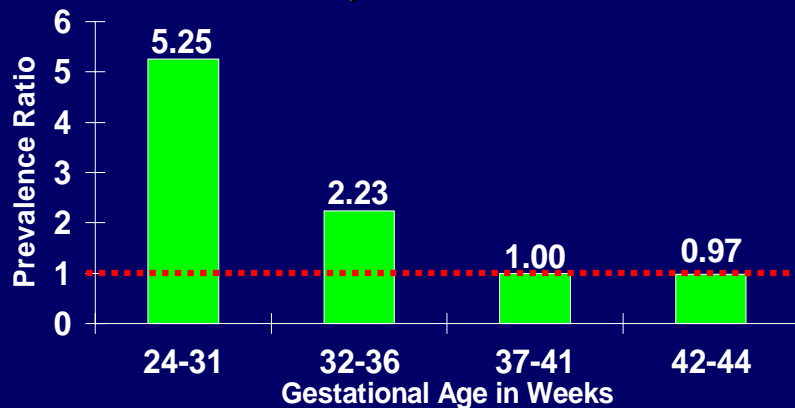
Shaw et al., *Paediatr Perinatal Epidemiol* 15:106-109, 2001

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**

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- 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**

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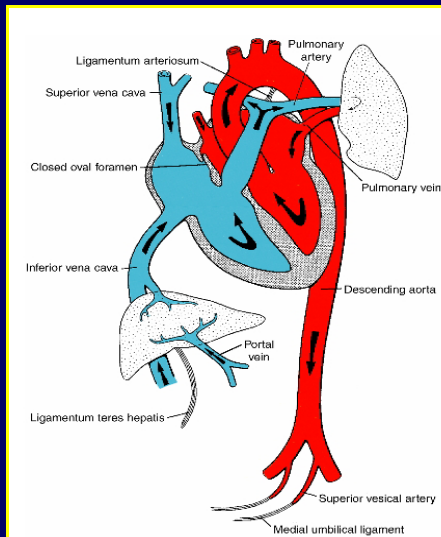
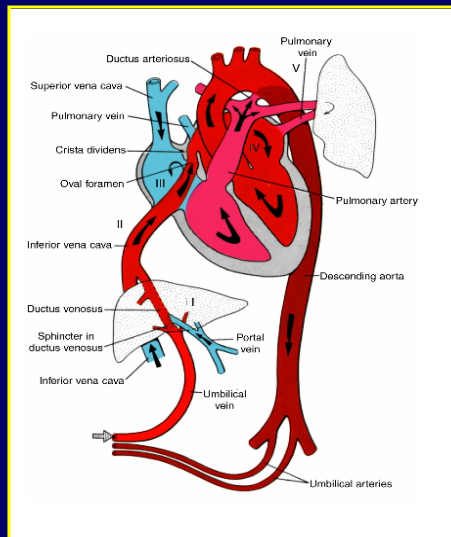
- **Structure necessary for  
intrauterine survival**
- **Infant delivered or pregnancy  
terminated before development  
complete**

## Developmentally Normal Conditions in the Preterm Infant

- Absent/decreased ear cartilage
- Blue sclera
- Large fontanel
- 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

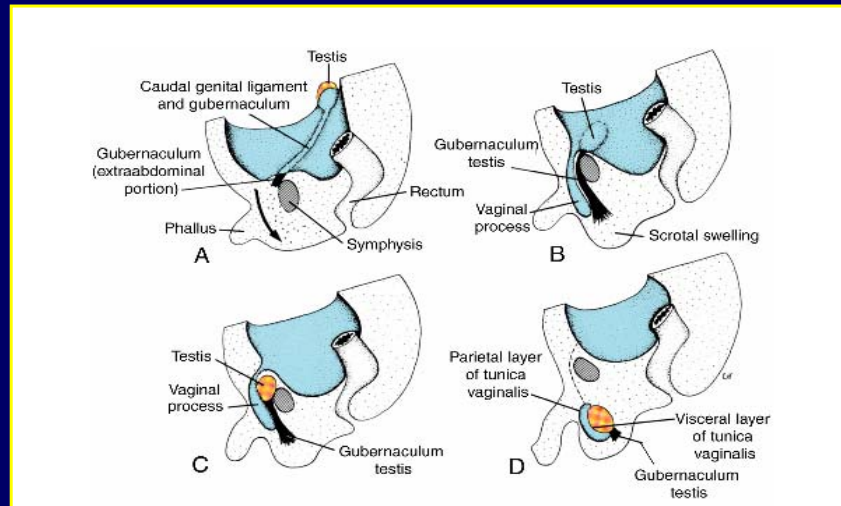
- Full-term infants
  - Closure in 50% by 24 hours, 90% by 48 hours, all by 72 hours
- Preterm infants
  - 30-36 weeks – incidence of PDA beyond 4 days – 11%
  - < 30 weeks – incidence of PDA beyond 4 days – 65%



Sadler TW, Langman's Medical Embryology, 10<sup>th</sup> edition, 2006

## 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 28<sup>th</sup> 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, 10<sup>th</sup> 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**

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- 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)**

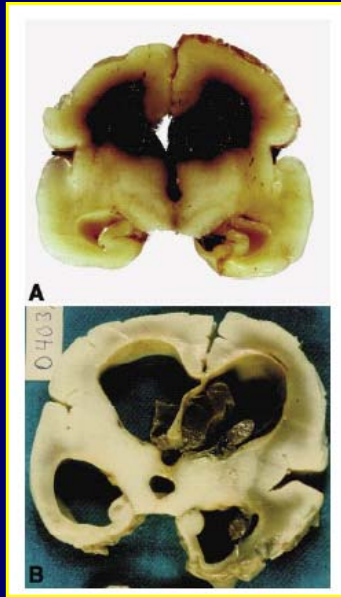
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- Up to 80% of infants born 23-24 weeks gestation develop IVH arising from periventricular germinal matrix (PGM)
- PGM established early in brain development – site of differentiation of neurons and glia, nearly disappears by 35-36 weeks

## **Hydrocephalus secondary to Intraventricular Hemorrhage (IVH)**

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- 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
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