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

- 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

- Birth defects: 20.4%
- Short gestation/LBW: 16.9%
- SIDS: 7.5%
- Maternal pregnancy complications: 5.9%
- Placenta, cord, membranes complications: 3.9%

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; Marian F. MacDorman, PhD; Sonja A. Rasmussen, MD, MS; Cheng Qin, MD, DrPH; Ewe M. Lackritz, MD

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 (≥ 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982</td>
<td>9.5</td>
</tr>
<tr>
<td>1992</td>
<td>10.7</td>
</tr>
<tr>
<td>2002</td>
<td>12.1</td>
</tr>
<tr>
<td>2003</td>
<td>12.3</td>
</tr>
<tr>
<td>2004</td>
<td>12.5</td>
</tr>
<tr>
<td>2005</td>
<td></td>
</tr>
</tbody>
</table>

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
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. Pauletti, 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

<table>
<thead>
<tr>
<th>Gestational Age in Weeks</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-28</td>
<td>2.8</td>
</tr>
<tr>
<td>29-32</td>
<td>3.4</td>
</tr>
<tr>
<td>33-34</td>
<td>2.6</td>
</tr>
<tr>
<td>35-36</td>
<td>2.0</td>
</tr>
<tr>
<td>37-41</td>
<td>1.0</td>
</tr>
<tr>
<td>42-45</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Rasmussen et al., J Pediatr 138:668-73, 2001
## Types of Birth Defects and Risk for Preterm Birth

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

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

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## Role of structural birth defects in preterm delivery

Gary M. Shaw*, David A. Savitz*, Verne Nelson* and John M. Thorp Jr*

*March of Dimes Birth Defects Foundation, California Birth Defects Monitoring Program, Oakland, CA. Department of Epidemiology, University of North Carolina School of Public Health, Chapel Hill, Carol G. Kersh Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

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

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

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 · Joani 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**

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 fontanels
- 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
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
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

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• Motoko Oinuma
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