ISSUES RELATED TO INFANT MORTALITY RATE
“Genetic” problems
- chromosomal anomalies
  (e.g. Trisomy 21, Trisomy 13, Trisomy 18)
- single gene mutations
  (e.g. phenylketonuria, cystic fibrosis)
- multifactorial disorders
  (environment + 2 or more mutant genes of small effect)
  (e.g. congenital heart disease)

“Baby” problems
- hydrops fetalis
- syndromes / sequences
  (e.g. Potter (oligohydramnios) sequence)
- “preemies”
- growth abnormalities

“Tumors”
The Four Life Spans

1. Neonatal (the dangerous first 4 weeks)
2. Infancy (the first year of life)
3. Age 1-4 years
4. Age 5-14 years
### Death Rates By Age / 1,000 Live Births

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Death Rate (1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 1 year*</td>
<td>7.3</td>
</tr>
<tr>
<td>1-4 years</td>
<td>0.3</td>
</tr>
<tr>
<td>5-14 years</td>
<td>0.2</td>
</tr>
<tr>
<td>15-24 years</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Infant Death Rate decreased from 20/1000 in 1970 to 7/1000 in 2000 – but with an unfortunate racial divide!
Infant mortality rates
US, 1993-2003

- In the US in 2003, 27,995 infants died before reaching their first birthday, an infant mortality rate of 6.8 per 1,000 live births.

- Between 1993 and 2003, the infant mortality rate in the US declined 19%.
Infant Mortality Rate (2000)

Of the 23 richest countries in the world, the US has the highest infant mortality rate.
Rankings of Infant Mortality

1960
- Sweden
- Netherlands
- Norway
- Czech Republic
- Australia
- Finland
- Switzerland
- Denmark
- England, Wales
- New Zealand
- Belgium
- United States
- Scotland
- N. Ireland
- Canada
- France
- Slovakia
- Ireland
- Japan
- Israel
- Singapore
- Germany
- Cuba
- Austria
- Greece
- Hong Kong
- Puerto Rico
- Spain
- Italy
- Bulgaria
- Hungary
- Poland
- Costa Rica
- Romania
- Portugal
- Chile

Country rankings
Lowest mortality rate

2004
- Singapore
- Hong Kong
- Japan
- Sweden
- Norway
- Finland
- Spain
- Czech Republic
- France
- Portugal
- tie: Netherlands
- Germany
- Greece
- Italy
- Switzerland
- Belgium
- Denmark
- tie: Israel
- Austria
- Australia
- tie: Ireland
- Scotland
- England, Wales
- Canada
- N. Ireland
- New Zealand
- Cuba
- Hungary
- tie: United States
- Slovakia
- Poland
- Puerto Rico
- Chile
- Costa Rica
- Russian Federation
- Bulgaria
- Romania

Highest mortality rate
Infant mortality rates by race
US, 2001-2003 Average

black infants were about 3 times as likely as Asian infants to die during the first year of life
Neonatal < 28 days

- congenital anomalies
- complications of preterm preterm delivery and LBW

Post-neonatal 28 days – 1 year

- SIDS
- congenital anomalies
CULTURAL COMPETENCE AND SUDDEN INFANT DEATH SYNDROME AND OTHER INFANT DEATH: A Review of the Literature from 1990 to 2000
Infant mortality by cause of death
US, 2003

Some of the leading causes of infant death include:
- Birth defects: 20%
- Prematurity/low birth weight (LBW): 17%
- Sudden infant death syndrome (SIDS): 8%
- Respiratory distress syndrome (RDS): 3%
- Maternal complications of pregnancy: 6%
### Infant Death in the US
#### The “Top 10” Causes in 2002

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Rank</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td>1</td>
<td>28,034</td>
<td>100</td>
</tr>
<tr>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>1</td>
<td>5,623</td>
<td>20.1</td>
</tr>
<tr>
<td>Disorders related to short gestational age and low birth weight, not elsewhere classified</td>
<td>2</td>
<td>4,637</td>
<td>16.5</td>
</tr>
<tr>
<td>SIDS</td>
<td>3</td>
<td>2,295</td>
<td>8.2</td>
</tr>
<tr>
<td>Newborn affected by maternal complications of pregnancy</td>
<td>4</td>
<td>1,708</td>
<td>6.1</td>
</tr>
<tr>
<td>Newborn affected by complications of placenta, cord, and membranes</td>
<td>5</td>
<td>1,028</td>
<td>3.7</td>
</tr>
<tr>
<td>Accidents</td>
<td>6</td>
<td>946</td>
<td>3.4</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>7</td>
<td>943</td>
<td>3.4</td>
</tr>
<tr>
<td>Bacterial sepsis of the newborn</td>
<td>8</td>
<td>749</td>
<td>2.7</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>9</td>
<td>667</td>
<td>2.4</td>
</tr>
<tr>
<td>Intrauterine hypoxia and birth asphyxia</td>
<td>10</td>
<td>583</td>
<td>2.1</td>
</tr>
<tr>
<td>All other causes</td>
<td></td>
<td>8,855</td>
<td>31.4</td>
</tr>
</tbody>
</table>
Infant mortality rates by maternal age
US, 2001-2003 Average

Infant mortality rates were highest for women under age 20 and ages 40 and older
### Percentage of fetal deaths and live births with selected characteristics, United States, 2003

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Non-Hispanic white</th>
<th>Non-Hispanic black</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mother's characteristics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 20 years of age</td>
<td>12.2</td>
<td>9.3</td>
<td>16.3</td>
</tr>
<tr>
<td>40 years of age and over</td>
<td>4.6</td>
<td>5.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Unmarried</td>
<td>46.8</td>
<td>32.4</td>
<td>72.7</td>
</tr>
<tr>
<td><strong>Fetal or infant characteristics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 1,500 grams</td>
<td>59.1</td>
<td>57.1</td>
<td>65.1</td>
</tr>
<tr>
<td>Less than 2,500 grams</td>
<td>73.9</td>
<td>71.6</td>
<td>79.6</td>
</tr>
<tr>
<td>4,000 grams or more</td>
<td>1.6</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Period of gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 32 weeks</td>
<td>62.7</td>
<td>60.6</td>
<td>69.4</td>
</tr>
<tr>
<td>Preterm (less than 37 weeks)</td>
<td>80.3</td>
<td>78.7</td>
<td>85.7</td>
</tr>
<tr>
<td>Plural delivery</td>
<td>9.1</td>
<td>10.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1,148</td>
<td>1,118</td>
<td>1,163</td>
</tr>
</tbody>
</table>
SANDRA D. LANE

WHY ARE OUR BABIES DYING?
Pregnancy, Birth, and Death in America

Eliminate Disparities in Infant Mortality

“Every Baby Deserves A First Birthday”

What can Healthcare Providers do to Help Reduce Infant Mortality Rates?

Health care providers should advise their patients about factors that affect birth outcomes, such as maternal smoking, drug and alcohol abuse, poor nutrition, stress, insufficient prenatal care, chronic illness or other medical problems.

What can Communities and Individuals do to Help Reduce Infant Mortality Rates?

Communities can play an important role in this effort by encouraging pregnant women to seek prenatal care in the first trimester and educating communities, providers, pregnant women and family members on factors that effect infant mortality such as smoking, substance abuse, poor nutrition, lack of prenatal care, medical problems, chronic illness, and sudden infant death syndrome (SIDS).
Fetal Death

The death of a formed fetus is one of the most emotionally devastating events for parents and clinicians.

- **Pregnancy loss** is one of the most common obstetric complications, affecting >30% of conceptions.

- Most of these occur **early** in gestation, are due to problems with implantation and may **not** be clinically apparent.

- However, 10–15% of conceptions result in clinically recognized pregnancy loss:
  - the majority of these are **1st trimester miscarriages**.
  - <5% of pregnancies are lost **after 10 weeks** of gestation.

- These later losses (**fetal deaths**) are particularly emotionally devastating for families and clinicians.
the rate of fetal death in the US decreased substantially in the mid-20th century, due to improved care for conditions such as RhD alloimmunization, maternal diabetes, preeclampsia, however, the past several decades have seen much greater reductions in neonatal death rates than in fetal death rates. Fetal death remains a significant and understudied problem that now accounts for almost 50% of all perinatal deaths.
Fetal Death

**risk factors** for fetal death include
- African American **race**
- advanced maternal **age**
- **obesity**
- **smoking**
- prior fetal death
- maternal diseases
  - diabetes
  - hypertension
  - red cell alloimmunization
  - antiphospholipid syndrome
- **fetal growth impairment (IUGR)**

**causes** of fetal death are numerous, and include
- **genetic** conditions
- **infections**
- placental abnormalities
- fetal–maternal hemorrhage
Childhood Mortality

- in the US around 1 newborn in 60 does not reach age 15
  - the majority of these are due to **birth defects** and **prematurity**
  - a significant minority (around 1 in 300) will die in an “**accident**”

- the true number of deaths from **SIDS** (Sudden Infant Death Syndrome) and **child abuse** is probably similar (1 kid in 6 coming to the emergency room is there because of injuries inflicted by an adult)

- **cancer** kills around 1 child in 2000
Childhood Mortality

- in the US around 1 newborn in 60 does not reach age 15

- the major killers of neonates and infants are **prematurity** and **birth defects**
  - around 1% of US newborns die from these causes
  - the causes of **premature labor** remain elusive, as is the mystery of why it's so much more common in the underclass
  - **birth defects** cause death in around 1 in 350 kids during the first year of life

- a significant minority (around 1 in 300) will die in an “**accident**”

- the true number of deaths from **SIDS** (**S**udden **I**nfant **D**eath **S**yndrome) and **child abuse** is probably similar (1 kid in 6 coming to the emergency room is there because of injuries inflicted by an adult)
  - ? up to 0.5% of infants during the 1st year of life

- **cancer** kills around 1 child in 2000
Infant Mortality Causes

- Congenital Anomalies: 19.6%
- Preterm Birth/ Low Birthweight: 15.7%
- Sudden Infant Death Syndrome: 9.5%
- Pregnancy Complications: 5.0%
- Respiratory Distress Syndrome: 4.0%

* Note: Because many birth defects are not identified at birth this number is an underestimate.
A **congenital** disease or **malformation** is any abnormality present at birth, even if not detected until after birth and encompasses all abnormalities caused by disturbed prenatal development, regardless of their nature. Congenital defects are found in **2 to 3%** of newborns. And 2 to 3% of developmental defects not recognized at birth become apparent as the child grows. Major malformations are found in 25 to 50% of spontaneously aborted embryos, fetuses and stillborns.

**Four major factors that induce congenital malformations:**

1. **Chromosomal** abnormalities
2. Abnormalities of individual **genes**
3. **Intrauterine injury** by drugs, radiation, maternal infection, or environmental factors
4. **Environmental** factors acting on a genetically predisposed embryo
Chromosomal Abnormalities In Perinatal Medicine

- thought to be the #1 cause of spontaneous abortions (SABs)
- account for ~50% of clinically recognized early pregnancy losses (i.e. “miscarriages”)
- at least 10% of conceptions have a chromosomal abnormality
  - at least 95% of these are lost before term

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Type of Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%</td>
<td>trisomies</td>
</tr>
<tr>
<td>20%</td>
<td>monosomies</td>
</tr>
<tr>
<td>15%</td>
<td>triploids</td>
</tr>
</tbody>
</table>
Chromosomal Abnormalities In Perinatal Medicine

- **autosomal trisomies**
  - most common = trisomy 21 (Down syndrome)
    - ~1 out of every 1000 live births
  - trisomy 18 (Edwards syndrome)
  - trisomy 13 (Patau syndrome)

- **sex chromosome aneuploidies** compatible with survival in most cases include:
  - 47,XXY (Klinefelter syndrome)
  - trisomy X (“super-female”)
  - 47,XYY

- **monosomy X (Turner syndrome)** is a frequent cause of pregnancy loss
  - only ~1% of 45,X conceptuses survive to term

chromosomal defects compatible with life but causing significant morbidity occur in ~0.5% of newborns
Half of First Trimester Spontaneous Abortions Are Aneuploid

50% autosomal trisomy*
  trisomy 16
  trisomy 22

25% polyploid
  triploid, etc.

20% sex chromosome monosomy
  XO

* Down syndrome (T21), Patau syndrome (T13) and Edwards syndrome (T18) are the only three trisomies compatible with extrauterine life !!
Congenital Anomalies

Definitions

- Morphologic defects that are present at birth
  - Some may not become clinically apparent until years later
    - E.g., cardiac defects and renal anomalies
- About 3% of newborns have a major anomaly
  - An anomaly having either cosmetic or functional significance
  - The most common cause of mortality in the 1st year of life
  - Contribute significantly to morbidity and mortality throughout the early years of life
- Anomalies found in live-born infants represent the less serious developmental failures in embryogenesis that are compatible with live birth
  - About 20% of fertilized ova are so anomalous that they are blighted from the outset
  - Others may be compatible with early fetal development, only to lead to spontaneous abortion
  - Less severe anomalies allow more prolonged intrauterine survival
    - Some disorders terminate in stillbirth
    - Those still less significant permit live birth despite the handicaps imposed
Congenital Malformations

- result from:
  - chromosomal problems
  - genes of large effect
  - deletions of chunks of a chromosome
  - polygenic problems
- or "just happen"
- range from familiar, correctable problems like (e.g. mild hypospadias) to dread, lethal conditions (e.g. anencephaly)
- at least 3% of kids have a “major” malformation (i.e. at least of serious cosmetic importance)
# Congenital Malformations

## Etiology

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendelian Disorders - Single Gene</td>
<td>20%</td>
</tr>
<tr>
<td>e.g. achondroplasia; cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Chromosomal Disorders</td>
<td>10%</td>
</tr>
<tr>
<td>e.g. trisomies (13, 18, 21); Turner syndrome</td>
<td></td>
</tr>
<tr>
<td>Environmental Causes - Teratogens</td>
<td>5%</td>
</tr>
<tr>
<td>Infections</td>
<td>1%</td>
</tr>
<tr>
<td>Maternal Disorders</td>
<td>1-2%</td>
</tr>
<tr>
<td>Therapeutic Radiation</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Drugs and Chemicals</td>
<td>2%</td>
</tr>
<tr>
<td>Unknown Cause and Multifactorial Malformations</td>
<td>65%</td>
</tr>
</tbody>
</table>

100%
Congenital Malformations

Causes

Genetic
- **gross chromosomal aberrations**
  - due to defective gametogenesis (egg and sperm)
  - most die *in utero*
  - e.g. Down, Patau, Edwards, Turner
- **single mutant genes**
  - autosomal dominant, autosomal recessive, or X-linked patterns of inheritance
- **polygenic or multifactorial**
  - accounts for the tendency toward recurrence within families

Environmental
- **viruses**
  - e.g. rubella → cataracts, heart defects, deafness
  - e.g. CMV → microcephaly, mental retardation
- **drugs and chemicals**
  - e.g. thalidomide → phocomelia
  - e.g. alcohol → fetal alcohol syndrome
  - e.g. phenytoin, folate antagonists, retinoic acid
- **radiation**
  - microcephaly, blindness, spina bifida
<table>
<thead>
<tr>
<th>Malformation</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>common clubfoot</td>
<td>1 in 400 children</td>
</tr>
<tr>
<td>patent ductus arteriosus</td>
<td>1 in 600 children</td>
</tr>
<tr>
<td>pyloric stenosis</td>
<td>1 in 600 children*</td>
</tr>
<tr>
<td>ventricular septal defect</td>
<td>1 in 1000 children</td>
</tr>
<tr>
<td>cleft lip (with or without cleft palate)</td>
<td>1 in 1000 children</td>
</tr>
<tr>
<td>meningocele /meningomyelocele</td>
<td>1 in 2000 children</td>
</tr>
<tr>
<td>anencephaly</td>
<td>1 in 3000 children</td>
</tr>
<tr>
<td>atresia of anus or other portion of gut</td>
<td>1 in 3000 children</td>
</tr>
</tbody>
</table>

*more common in boys
Common Congenital Malformations
Congenital Anomalies
Definitions

agenesis  absence of organ or primordium
aplasia  absence of organ due to failure of primordium
atresia  absence of an opening
hypoplasia  incomplete development of an organ
hyperplasia  overdevelopment of an organ
hypertrophy  increase in cell size in organ or tissue
hypotrophy  decrease in cell size in organ or tissue
dysplasia  abnormal cell organization
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>agenesis</td>
<td>absence of an organ or tissue due to failure of the primordium to develop during embryogenesis</td>
</tr>
<tr>
<td>aplasia</td>
<td>absence of all or part of an organ or tissue owing to defective development of the primordium</td>
</tr>
<tr>
<td>atresia</td>
<td>absence of an opening, usually of a hollow visceral organ (e.g. trachea; intestine)</td>
</tr>
<tr>
<td>hypoplasia</td>
<td>incomplete development or underdevelopment of an organ with decreased numbers of cells</td>
</tr>
<tr>
<td>hyperplasia</td>
<td>overdevelopment of an organ with increased numbers of cells</td>
</tr>
<tr>
<td>hypertrophy</td>
<td>an abnormality in an organ or a tissue as a result of an increased size (rather than the number) of individual cells</td>
</tr>
<tr>
<td>hypotrophy</td>
<td>an abnormality in an organ or a tissue as a result of a decreased size (rather than the number) of individual cells</td>
</tr>
<tr>
<td>dysplasia</td>
<td>an abnormal organization of cells</td>
</tr>
</tbody>
</table>
thumb agenesis  thymic aplasia  duodenal atresia  pulmonary hypoplasia

adrenal hyperplasia  pyloric hypertrophy  muscle hypotrophy  renal dysplasia
## Congenital Malformations

### Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>malformation</td>
<td>intrinsic abnormality occurring during development</td>
<td>congenital heart defects</td>
</tr>
<tr>
<td>deformation</td>
<td>structural abnormality secondary to mechanical factors</td>
<td>clubfeet</td>
</tr>
<tr>
<td>disruption</td>
<td>secondary abnormality of an organ or body region that was previously normal</td>
<td>intestinal atresia due to intrauterine vascular accident; amniotic bands</td>
</tr>
<tr>
<td>sequence</td>
<td>constellation of abnormalities secondary to a single localized initiating defect</td>
<td>oligohydrarnnios sequence → fetal compression → altered facies/pulmonary hypoplasia/hand and foot deformities</td>
</tr>
<tr>
<td>syndrome</td>
<td>constellation of anomalies that are related, but cannot be explained on the basis of a single localized defect</td>
<td>viral infection; chromosomal aberrations</td>
</tr>
</tbody>
</table>
Types of Problems in Morphogenesis

- Poor formation of tissue: Malformation or Malformation sequence
- Unusual forces on normal tissue: Deformation or Deformation sequence
- Breakdown of normal tissue: Disruption or Disruption sequence
- Abnormal organization of cells in tissue: Dysplasia or Dysplasia sequence
Congenital Anomalies
Definitions

- **malformations** represent primary errors of morphogenesis (i.e. an *intrinsically* abnormal developmental process)
  - usually **multifactorial** rather than the result of a single gene or chromosomal defect
  - may present in several patterns
    - involve **single body systems** (e.g. congenital heart defects and anencephaly)
    - **multiple** malformations involving many organs may coexist
Congenital Anomalies

Definitions

- **deformations** result from an *extrinsic* disturbance of development rather than an intrinsic error of morphogenesis
  - common problems
    - affect approximately 2% of newborn infants to varying degrees
  - localized or generalized compression of the growing fetus by *abnormal biomechanical forces*, leading eventually to a variety of structural abnormalities
    - the most common underlying factor is *uterine constraint*
      - between the **35th and 38th weeks** of gestation → rapid increase in the size of the fetus outpaces the growth of the uterus → relative amount of *amniotic fluid* (which normally acts as a “cushion”) also decreases → even the normal fetus is subjected to some form of uterine constraint
  - several factors increase the likelihood of excessive compression of the fetus resulting in deformations
    - **maternal factors**
      - first pregnancy
      - small uterus
      - malformed (bicornuate) uterus
      - leiomyomas
    - **fetal or placental factors**
      - oligohydramnios
      - multiple fetuses
      - abnormal fetal presentation (e.g. breech)
**Congenital Anomalies**

**Definitions**

- **disruptions** result from **secondary destruction** of an organ or body region that was previously normal in development (i.e. an **extrinsic disturbance in morphogenesis**)
  - **amniotic bands** (rupture of amnion with resultant formation of "bands" that encircle, compress, or attach to parts of the developing fetus)
  - a variety of **environmental agents** may cause disruptions

- **not heritable** → not associated with risk of recurrence in subsequent pregnancies
DISRUPTION

“A morphologic defect resulting from extrinsic interference with a normal process.”

amniotic band
Disruption
Amniotic Bands

fetal foot with digital amputations
and associated amniotic bands
Amniotic Band
Amniotic Band Sequence

- A sequence of mechanically-induced disruptions of fetal organ systems and/or extremities
- Caused by cords and sheets of tissue adhesions between the fetal membranes and the embryo

- Rupture of amniotic sac
- Full or partial prolapse of embryo into the chorionic cavity
- Adhesions between fetal structures and placenta
- Adhesions “ensnare” and constrain the embryo
- Traction on embryo
- Impaired/deformed organ field development
Congenital Anomalies

**Definitions**

- **sequence** is a pattern of “cascade” anomalies
  - about half the time, congenital anomalies occur singly
  - in the remaining cases, **multiple** congenital anomalies are recognized
  - in some cases, multiple anomalies may be explained by a single, localized aberration in organogenesis (malformation, disruption, or deformation) leading to secondary effects in other organs
  - e.g. **oligohydramnios (or Potter) sequence**
    - oligohydramnios (↓ amniotic fluid) may be caused by a variety of unrelated maternal, placental, or fetal abnormalities
    - chronic leakage of amniotic fluid because of rupture of the amnion (pPROM, prolonged premature rupture of membranes)
    - uteroplacental insufficiency resulting from maternal hypertension or severe toxemia
    - **renal agenesis** in the fetus (**fetal urine** is a major constituent of amniotic fluid)
  - **fetal compression** associated with significant oligohydramnios, in turn, results in a **classic phenotype** in the newborn infant, including
    - flattened facies
    - positional abnormalities of the hands and feet
    - dislocated hips may be dislocated
    - compromised growth of the chest wall and the contained lungs → hypoplastic lungs → fetal demise
  - nodules in the amnion (**amnion nodosum**) are frequently present
SEQUENCE

“A pattern of anomalies derived from a known (or presumed) malformation or mechanical factor.”

prune belly

“cascade of anomalies”
"Deformation Through Constraint"

Diagram showing the relationship between oligohydramnios and fetal compression resulting in various fetal anomalies such as renal agenesis, amniotic leak, pulmonary hypoplasia, altered facies, positioning defects of feet, hands, and breech presentation.
"Deformation Through Constraint"
“Deformation Through Constraint”

normal

oligohydramnios
POTTER'S SYNDROME
The Consequences of Renal Agenesis

- Normal development happens at about 31 days.
- Defective development.

- **RENAL AGENESIS**
- Lack of urine into amniotic cavity.
- Relative lack of amniotic fluid during fetal life.

- Abnormal positioning of hands and feet.
- Altered facies.
- Death from respiratory insufficiency.
- Pulmonary hypoplasia.
- Breech presentation.
- Amnion nodosum.

- Death from respiratory insufficiency.
Oligohydramnios Sequence

Facial Dysmorphism

- folds inferior to the eyelids
- small chin
- “parrot beak” nose
- prominent earlobes
- Suborbital grooves extending from the epicanthal regions to the malar regions bilaterally.
- The nasal appearance has been described as that of “a nose pressed against a plate glass window” and viewed from the other side.

- Flattened nasal tip.
- Abnormal ear lobation.
- Micrognathia (“small chin”).
“Deformation Through Constraint”
“Deformation Through Constraint”
Prune Belly Sequence

- congenital disorder of the urinary system
- named for the mass of wrinkled skin that is often (but not always) present on the abdomens of those with the disorder
- 20% mortality
- 1:40,000 live births
- M:F = 20:1
Prune Belly Sequence

- characterized by a **triad** of symptoms
  1. partial or complete **lack** of *abdominal muscles*
     - there may be wrinkly folds of skin covering the abdomen
  2. **undescended testes** (cryptorchidism) in males
  3. urinary tract anomalies
     - unusually **large ureters**
     - **distended bladder**
     - accumulation and **backflow of urine** from the bladder to the ureters and the kidneys
developmental *mesodermal arrest* explains the involvement of the *genitourinary tract*, *testis*, and *abdominal wall muscles*

children with prune belly sequence can present with myriad *renal, ureteral, and urethral* abnormalities

- *posterior urethral valves*
- obstruction and/or upper urinary tract dilatation
- *cystic / dysplastic kidneys*

**abdominal wall hypoplasia**: lack of abdominal muscles leads to a poor cough mechanism, which, in turn, leads to increased pulmonary secretions

- *pulmonary hypoplasia*
- weak abdominal muscles also lead to constipation because of an inability to perform the Valsalva maneuver
hypoplastic right lung

hypoplastic left lung
Prune Belly Sequence

- large and redundant bladder (megacystis)
  - a patent urachus is the means by which patients are able to survive
- elongated, dilated, and tortuous megaureters
- undescended (cryptorchid) testes
- orthopedic anomalies
  (e.g. scoliosis, congenital hip dislocation)
- GI anomalies
  (e.g. malrotation, atresia, stenosis, and volvulus)
Potter Sequence

the kidneys normally produce the amniotic fluid (as urine)

- a complex of findings associated with a lack of amniotic fluid (oligohydramnios) and kidney failure that develops before an infant is born
- the primary defect is kidney failure that occurs before the baby is born, either from
  - failure of the kidneys to develop
    - bilateral renal agenesis
      - 1:3,000 live births
      - 20% of Potter cases
  - other diseases that cause the kidneys to fail
    - renal hypoplasia
    - polycystic kidney disease
    - posterior urethral valves
Bilateral (Complete) Renal Agenesis in Potter Sequence

large fetal adrenal glands
the typical Potter phenotype (appearance) is determined by the **absence of amniotic fluid (oligohydramnios)**

- the infant is not “cushioned” from the walls of the uterus
  (→ “deformation through constraint”)
- the pressure of the uterine wall causes a typical facial appearance (**Potter facies**) that includes
  - **widely separated eyes** with prominent suborbital folds
  - **broad nasal bridge**
  - **low-set ears**
  - **receding chin**

- because of limited space in the uterus, the limbs may be abnormal, or held in abnormal positions (e.g. talipes equinovarus) or **contractures**
- oligohydramnios also stops development of the lungs (**hypoplastic lungs**)
Amnion Nodosum

- multiple, firm, circumscribed, round to ovoid, raised, shiny, **yellow nodules**, ranging from 1 to 5 mm in diameter, visible **on the amniotic surface**

- **squamous cells** (occasionally keratinized) embedded in degenerative amorphous acidophilic granular debris, attached to the **fetal surface** of the **amniotic epithelium**
  - the process is largely **superficial** and the underlying stroma does **not** participate in the formation of the lesion

- represents deposits of squamous cell elements from the **fetal skin** accumulating and organizing on the surface of the amniotic epithelium and undergoing secondary degenerative changes

Unlike any other single placental feature, amnion nodosum is associated with an extremely high risk of fetal and perinatal mortality (35%).

This outcome is due mainly to lethal congenital malformations, predominantly of the genitourinary system (e.g. renal agenesis) and **oligohydramnios**-associated fetal pulmonary hypoplasia (**Potter sequence**).
Potter Sequence

Amnion Nodosum

small, granular, tan-yellow nodules of amorphous material (vernix caseosa) with embedded/impacted desquamated fetal skin cells (squames; keratin) in the amniotic epithelium
Amnion Nodosum
a syndrome is a “constellation” of congenital anomalies, “believed to be” pathologically related, that, in contrast to a sequence, cannot be explained on the basis of a single, localized, initiating defect

- most often caused by a single etiologic agent which simultaneously affects several tissues
  - viral infection
  - specific chromosomal abnormality
    - e.g. trisomy 18 (Edwards syndrome)
SYNDROME

“A recognizable pattern of anomalies which is known or thought to be causally related”

“group of anomalies due to a single cause”

trisomy 21
folic acid from Latin *folium*, “leafy”

occurs naturally** in leafy vegetables (e.g. spinach, turnip greens, dried beans, and peas), but also in sunflower seeds, a variety of other fruits and vegetables, and ... liver

*especially prior to and during the first month following conception*

**some breakfast cereals are fortified with 25%-100% of the RDA for folic acid (400 μg/day), but keep in mind that the RDA for pregnant women is 600 μg/day*

supplementing the maternal diet with folic acid prior to (and during) pregnancy* can reduce the incidence of NTDs
Fetal Alcohol Syndrome (FAS)

- The most clinically recognizable form of fetal alcohol spectrum disorders (FASD)
- Caused by the effects of maternal alcohol consumption during pregnancy
  - Although more strongly associated with higher levels of alcohol consumption compared with lower levels, animal studies have suggested that even a single episode of consuming the equivalent of 2 alcoholic drinks during pregnancy may lead to loss of fetal brain cells
- May affect up to 1% of the US population
Fetal Alcohol Syndrome

Alcoholism during pregnancy is one of the most common and important causes of mental and physical retardation in the offspring. In severe cases of maternal alcohol abuse and dependence all of the child’s organs will show toxic effects with the full-blown picture of the fetal alcohol syndrome (FAS). Alcohol acts on the embryo and fetus: (1) as a cytotoxin, with pre- and postnatal growth disorders; (2) as a teratogen, with typical craniofacial changes and in some cases variable minor and major malformations; (3) as a neurotoxin with structural changes in the central nervous system (CNS), multiple cerebral dysfunctions and behavioral changes; and (4) by promoting addiction.

Fetal alcohol syndrome (FAS) is one of the most common, preventable causes of mental retardation in the world today. It may occur as often as Down’s syndrome and neural tube defects. FAS is estimated to occur in one to three cases per 1,000 individuals. At least one third to one half of children born to chronic alcoholic mothers show some signs of fetal alcohol syndrome. Although geographic and cultural differences affect the amount of alcohol a pregnant woman drinks, FAS occurs in all races and is more often a problem in developed countries.
Embryofetal Alcohol Syndrome
Criteria

- maternal alcohol abuse
- IUGR → LBW
- failure to thrive
- microcephaly
- motor and mental retardation with subsequent motor hyperactivity (hyperactive child syndrome)
- characteristic facies
  - epicanthal folds
  - drooping eyelids (ptosis)
  - foreshortened nose
  - nasolabial folds
  - small chin (micrognathia)
Fetal Alcohol Syndrome (FAS)

- characterized by a **pattern** of
  - **minor facial anomalies**
    - short palpebral fissures
    - thin upper lip
    - long, smooth philtrum
  - **other findings**
    - flat midface
    - ptosis of the eyelids
    - epicanthal folds
    - upturned nose with flat nasal bridge
    - underdeveloped ears
      ("railroad track" appearance)
    - clinodactyly of the fifth finger
    - "hockey stick" palmar creases
    - hirsutism
    - cardiac defects
- **prenatal and postnatal growth retardation**
  - typically results in a height or weight **below** the 10th percentile for age and race
- **functional or structural CNS abnormalities**
  - microcephaly is common
FAS
Facies

MOST FREQUENT
IN FAS

MORE FREQUENT
IN FAS

- Microcephaly
- Short palpebral fissures
- Flat midface
- Indistinct philtrum
- Thin upper lip
- Micrognathia
- Epicanthal folds
- Low nasal bridge
- Minor ear anomalies
- Short nose
Fetal Alcohol Syndrome (FAS)

- the consequences are **lifelong** !!!
- the behavioral and learning difficulties are often **greater** than the degree of neurocognitive impairment
- CNS impairment may **not** be apparent in newborns
  - average IQ attained = **63**
  - cognitive deficits and behavioral anomalies typically become **more apparent** in school-aged children and usually **persist** into adolescence and adulthood
  - e.g. attention-deficit/hyperactivity disorder [ADHD]
- facial findings may become **less characteristic** with advancing age
Fetal Alcohol Syndrome (FAS)

This syndrome is 100% preventable!!!

- the consequences are lifelong!!
- the behavioral and learning difficulties are often greater than the degree of neurocognitive impairment
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- facial findings may become less characteristic with advancing age
Diabetic Embryopathy

**maternal hyperglycemia** during time of embryogenesis has a **teratogenic effect** on the development of the embryo

- clinical diagnosis based on one or more congenital anomalies or fetal/neonatal complications in a baby that are attributed to his/her Mom’s diabetes
  - high blood glucose levels and ketones pass through the placenta to the baby, increasing the chance of birth defects
- maternal morbidity factors in diabetic pregnancies which can increase a baby's risk for birth defects:
  - ketoacidosis
  - polyhydramnios
  - preeclampsia
  - preterm labor
  - caesarean section*

*When extra sugar is in a mother's blood during pregnancy, the baby is "fed" extra sugar, too, leading to a bigger baby that is harder to deliver (macrosomia)
Diabetic Embryopathy

“Giant Babies”

“pasty”, swollen, obese constitution
due to reactive GH (somatotropin) secretion
Fetal Complications And Birth Defects Associated With Maternal Diabetes

**cardiac anomalies**
most commonly VSD or TGV

**DiGeorge anomaly**
due to abnormal neural crest cell migration
affects normal fetal development of the heart, thymus, and parathyroid glands

**NTDs**
due to maternal diabetic factors causing improper embryonic “folding”
most commonly spina bifida, anencephaly

**macrosomia**
occurs in ~ 1/3 of all diabetic pregnancies
can cause life-long obesity for child

**IUGR**
due to nutrient limitation associated with maternal hypotension

**SAB**
debated somewhat, but appears to be increased in pregnancies with poor diabetic control

**caudal regression**
agenesis of sacrum and lumbar spine; hypoplasia of lower extremities
due to improper embryonic “folding” caused by maternal diabetic factors

**abnormal postnatal neurologic development**
due to effects of ketosis
Perinatal And Neonatal Complications Associated With Maternal Diabetes

**fetal asphyxia** can cause **cerebral palsy** as well as affecting many other systems such as pulmonary, GI, and cardiovascular.

**preterm birth** can lead to **respiratory distress syndrome (RDS)**, occurs in ~ 30% of diabetic pregnancies, even when diabetic control has been meticulous.

**hypoglycemia** can cause **seizures, coma, and brain damage** if not recognized and treated quickly.

**hypocalcemia** and **hypomagnesemia** caused primarily by premature birth and its affects on **parathyroid** function.

**hyperbilirubinemia** caused primarily by premature birth.

**cardiomyopathy** and/or **cardiomegaly** most commonly seen in **macrosomic** infants of poorly controlled diabetic mothers.
Apgar Score for Newborns

- **simple** and repeatable method to **quickly** and summarily assess the health of newborns immediately after childbirth
- determined by evaluating the newborn baby on **5 simple criteria** on a **scale from 0 to 2** and summing up the 5 values thus obtained
- the 5 acronymic criteria are used as a **mnemonic** learning aid

**Appearance** (Skin color)
**Pulse** (Heart rate)
**Grimace** (Reflex irritability)
**Activity** (Muscle tone)
**Respiration**
Apgar Score for Newborns

- Apgar scores are calculated at 1 and 5 minutes
  - if there are problems with the baby an additional score is given at 10 minutes
- a score of 7-10 is considered normal, while 4-7 might require some resuscitative measures, and a baby with a score of \( \leq 3 \) and below requires immediate resuscitation

Apgar score of 0-1 at 5 minutes is associated with a mortality rate of 50% in the 1st month of life

Apgar score of 4 at 5 minutes is associated with a mortality rate of 20% in the 1st month of life

Apgar score of \( \geq 7 \) at 5 minutes is associated with a mortality rate of almost 0
But APGAR is not only an acronym*…

It’s also an eponym**!

* from the Greek *acro*-(tip) + *onuma* (name): a word formed from the initial letters of other words
** from the Greek *epi*-(upon) + *onuma* (name): a disease, structure, operation, or procedure named after (upon) the person who first discovered or described it
A Proposal for a New Method of Evaluation of the Newborn Infant.*

Virginia Apgar, M.D., New York, N.Y.

Department of Anesthesiology, Columbia University, College of Physicians and Surgeons and the Anesthesia Service, The Presbyterian Hospital

Resuscitation of infants at birth has been the subject of many articles. Seldom have there been such imaginative ideas, such enthusiasms, and dislikes, and such unscientific observations and study about one clinical picture. There are outstanding exceptions to these statements, but the poor quality and lack of precise data of the majority of papers concerned with infant resuscitation are interesting.

There are several excellent review articles but the main emphasis in the past has been on treatment of the asphyxiated or apneic newborn infant. The purpose of this paper is the reestablishment of simple, clear classification or "grading" of newborn infants which can be used as a basis for discussion and comparison of the results of obstetric practices, types of maternal pain relief and the effects of resuscitation.

The principle of giving a "score" to a patient as a sum total of several objective findings is not new and has been used recently in judging the treatment of drug addiction. The endpoints which have been used previously in the field of resuscitation are "breathing time" defined as the time from delivery of the head to the first respiration, and "crying time" the time until the establishment of a satisfactory cry. Other workers have used the terms mild, moderate and severe depression to signify the state of the infant. There are valid objections to these systems. When mothers receive an excessive amount of depressant drugs in the antepartum period, it is a common occurrence that the infants breathe once, then become apneic for many minutes. Evaluation of the breathing time is difficult. A satisfactory cry is sometimes not established even when the infant leaves the delivery room, and in some patients with cerebral injury, the baby dies without ever having uttered a satisfactory cry. Mild, moderate and severe depression of the infant leaves a fair margin for individual interpretation.

A list was made of all the objective signs which pertained in any way to the condition of the infant at birth. Of these, five signs which could be determined easily and without interfering with the care of the infant were considered useful. A rating of zero, one or two, was given to each sign depending on whether it was absent or present. A score of ten indicated a baby in the best possible condition. The time for judging the five objective signs was varied until the most practi-
Abnormal Size for Gestational Age

Too Big
Abnormal Size for Gestational Age
Abnormal Size for Gestational Age

Too Little
Abnormal Size for Gestational Age
Abnormal Size for Gestational Age
Low Birth Weight

- “tiny babies”: born at full term (37 weeks or later) but
  - low birth weight (LBW) < 2500 g (~ 5½ lb)
  - very low birth weight (VLBW) < 1500 g
  - extremely low birth weight (ELBW) < 1000 g
  - intrauterine growth restriction (IUGR): delayed growth within the uterus, which then leads to LBW

- caring for these babies is expensive and the outcomes uncertain
  - 1/3 of infants that die are LBW and another 1/3 are VLBW/ELBW
  - at school age, surviving LBW children still show signs of damage in all neurobehavioral parameters – except happiness
  - survivors often need long-term expensive care
  - it is not clear that intensive “interventions” to improve cognitive abilities do any good at all!

- survival has increased tremendously (thanks largely to surfactant!), with no decrease in incidence (due largely to low socioeconomic status)
  - “prenatal care prevents LBW”? → poverty itself (i.e. low socioeconomic class “behaviors”), and not inadequate prenatal care, is the overriding factor
# Birth Weight and Gestational Age

**term infants usually weigh ≥ 2500 grams**

**mortality risk is a function of birth weight and gestational age**

<table>
<thead>
<tr>
<th>AGA</th>
<th>birth weight <em>between</em> 10th - 90th percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Average for Gestational Age)</td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>birth weight &lt; 10th percentile</td>
</tr>
<tr>
<td>(Small for Gestational Age)</td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td>&gt; 90th percentile</td>
</tr>
<tr>
<td>(Large for Gestational Age)</td>
<td></td>
</tr>
<tr>
<td>Preterm</td>
<td>infants born <em>before</em> 37 weeks</td>
</tr>
<tr>
<td>Term</td>
<td>infants born <em>between</em> 37 - 42 weeks</td>
</tr>
<tr>
<td>Post-Term</td>
<td>infants born <em>after</em> 42 weeks</td>
</tr>
</tbody>
</table>
Large for gestational age (LGA) mortality higher than AGA

Appropriate for gestational age (AGA)

<1%

Small for gestational age (SGA) mortality higher than AGA

80%

20%

1%

Premature birth

% = Approximate neonatal death rate
Small for Gestational Age (SGA)

- may be preterm, full-term, or post term
- however, the defining characteristic specifies that they are small for their designated gestational age ("small for dates")
- **below 10th percentile** on the charts
- the child did not grow properly in the uterus, and the organs will have extra problems once the child is born
Small for Gestational Age (SGA)

- **problems with Mom**
  - inadequate prenatal care
  - cocaine ("crack babies")
  - tobacco
  - opiate abuse
  - alcoholism
  - hypertensive disorders of pregnancy (toxemia, preeclampsia, eclampsia)
Small for Gestational Age (SGA)

- problems with the placenta or uterus
  - infarcts
  - tumors
    - chorangioma
  - thrombophilias (clots in the spiral arteries and between the villi of the placenta)
  - etc., etc.
Small for Gestational Age (SGA)

- problems with the **unborn child** itself
  - constitutional (familial + racial background) (~ 80% of cases)
    - no increased perinatal death / morbidity
  - chromosomal problems
    - trisomy 21
    - trisomy 18
  - congenital infections ("TORCH")
  - toxoplasmosis
  - other (syphilis, etc.)
  - rubella
  - Cytomegalovirus (CMV)
  - Herpes (usually not an intra-uterine infection)
  - Listeria
    - like syphilis, passes through the placenta; less likely to produce actual deformities, though it can be very deadly
- other **congenital anomalies**
  - congenital heart disease
  - diaphragmatic hernia
  - tracheo-esophageal fistula
- being conceived by the **new reproductive technologies** (?? doubles the risk even when you control for twinning)
Small for Gestational Age (SGA)

Symmetric (Proportionate; Type I IUGR)
- all organs similarly affected
- short length but weight appropriate for length
- earlier intrauterine injury
  - chromosomal or congenital anomalies
  - infections

Asymmetric (Disproportionate; Type II IUGR)
- normal head, small body, brain spared
- later intrauterine injury
  - uteroplacental insufficiency
  - abruptio placentae
  - placenta previa
  - twins
  - maternal HTN
  - cigarette smoking
  - drugs

causes $>\frac{1}{3}$ of cases of IUGR
Small for Gestational Age (SGA)

- occur more frequently in SGA:
  - intrauterine fetal demise
  - perinatal asphyxia
    - SGA fetus tolerates labor poorly; often resuscitated at birth
  - respiratory distress
  - meconium aspiration
    - the fetus ingests amniotic fluid containing meconium, or it occurs when the neonate takes his first breath
    - it may cause atelectasis, pneumothorax, or pneumonitis
  - hypoglycemia
    - most likely to occur from 12 to 48 hours after birth
    - may lead to neurological damage
  - hypothermia
    - due to lack of subcutaneous fat
  - congenital anomalies
    - genitourinary and cardiovascular systems are most common
Large for Gestational Age (LGA)

- those whose birth weight places them above the 90th percentile of normal for their gestational age
  - most born at term
- maternal diabetes is by far the most common cause
- delivery problems (dystocia)
  - prolonged vaginal delivery time
  - difficult birth
  - increase in cesarean section
Large for Gestational Age (LGA)

- occur frequently in the LGA infant:
  - hypoglycemia
    - related to hyperinsulinism following birth
  - hypocalcemia
    - associated with prematurity or asphyxia
  - polycythemia
  - hyperbilirubinemia
  - respiratory distress syndrome
  - congenital anomalies
Intrauterine Growth Restriction (IUGR)

“undergrown but not necessarily premature”

- IUGR implies a downward deflection on a growth curve, requiring several measurements over time
- it is not the same as SGA
  - many SGA fetuses will be entirely normal, often termed "constitutionally small"
IUGR

Contributing Factors

**Fetal**
- congenital anomalies
- chromosomal aberrations
  - triploidy
  - trisomies (21, 18, 13)
- deletions
- translocations
- infections
  - CMV
  - rubella
  - syphilis
  - toxoplasmosis

**Placental**
- single umbilical artery
- abnormal cord insertion
- hemangioma
- placental infarction
- abruptio placentae
- placenta previa
- multiple fetuses
- infection
- confined placental mosaicism

**Maternal**
- pregnancy induced hypertension (PIH, toxemia of pregnancy)
  - preeclampsia
  - eclampsia
- chronic hypertension
- substance abuse
- alcoholism
- cigarette smoking
- malnutrition
Fetal Growth Restriction

- small-for-gestational-age (SGA) infants traditionally defined as those with birth weights below the 10th percentile for their gestational age
- one of the strongest risk factors for newborn encephalopathy
- not all infants with birth weights below the 10th percentile have pathologic growth restriction
  - some are small simply because of constitutional factors
- mortality and morbidity are increased among infants born at term whose birth weights are at or below the 3rd percentile for their gestational age
• approximately 10% of births in the United States are preterm (occurring before 37 weeks of gestation)
• preterm infants with "very low" birth weight are those who weigh 1500 g or less; those with "extremely low" birth weight weigh 1000 g or less
• although they account for only 1.5% and 0.7% of live births, respectively, these infants contribute disproportionately to neonatal morbidity and to health care costs
# Very Low Birth Weight “Preemies”

## Major Short- and Long-Term Problems

<table>
<thead>
<tr>
<th>Affected Organ or System</th>
<th>Short-Term Problems</th>
<th>Long-Term Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>Respiratory distress syndrome, air leak, bronchopulmonary dysplasia, apnea of prematurity</td>
<td>Bronchopulmonary dysplasia, reactive airway disease, asthma</td>
</tr>
<tr>
<td>Gastrointestinal or nutritional</td>
<td>Hyperbilirubinemia, feeding intolerance, necrotizing enterocolitis, growth failure</td>
<td>Failure to thrive, short-bowel syndrome, cholestasis</td>
</tr>
<tr>
<td>Immunologic</td>
<td>Hospital-acquired infection, immune deficiency, perinatal infection</td>
<td>Respiratory syncytial virus infection, bronchiolitis</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Intraventricular hemorrhage, periventricular white-matter injury, hydrocephalus</td>
<td>Cerebral palsy, hydrocephalus, cerebral atrophy, neurodevelopmental delay, hearing loss</td>
</tr>
<tr>
<td>Ophthalmologic</td>
<td>Retinopathy of prematurity</td>
<td>Blindness, retinal detachment, myopia, strabismus</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, patent ductus arteriosus, pulmonary hypertension</td>
<td>Pulmonary hypertension, hypertension in adulthood</td>
</tr>
<tr>
<td>Renal</td>
<td>Water and electrolyte imbalance, acid–base disturbances</td>
<td>Hypertension in adulthood</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Iatrogenic anemia, need for frequent transfusions, anemia of prematurity</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypoglycemia, transiently low thyroxine levels, cortisol deficiency</td>
<td>Impaired glucose regulation, increased insulin resistance</td>
</tr>
</tbody>
</table>
## Birth defect risk doubles in pre-term babies

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Number of infants with birth defects</th>
<th>Total live births</th>
<th>Prevalence per 1,000 births</th>
<th>Adjusted prevalence ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24–31</td>
<td>11,804</td>
<td>76,143</td>
<td>155.02</td>
<td>5.25 (5.15–5.35)</td>
</tr>
<tr>
<td>32–36</td>
<td>30,225</td>
<td>453,859</td>
<td>66.60</td>
<td>2.23 (2.21–2.26)</td>
</tr>
<tr>
<td>24–36 (all preterm)</td>
<td>42,029</td>
<td>530,002</td>
<td>79.30</td>
<td>2.65 (2.62–2.68)</td>
</tr>
<tr>
<td>37–41</td>
<td>184,053</td>
<td>6,226,677</td>
<td>29.56</td>
<td>Referent</td>
</tr>
<tr>
<td>42–44</td>
<td>3,658</td>
<td>126,903</td>
<td>28.83</td>
<td>0.97 (0.94–1.01)</td>
</tr>
</tbody>
</table>

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

---

National Center on Birth Defects and Developmental Disabilities (NCBDDD)
“Preemie”

- born **before 37-38** weeks
- about 1 birth in 10 in the US
- etiology often obscure
- many statistical correlations, few “why”’s that make sense
  - birth defects involving the uterus
  - preterm premature rupture of membranes (pPROM), with possible infection
  - placenta previa or abruptio placentae
  - smoking
  - hypertension
  - poverty
  - very young or very old Mom
“Preemie” Outcomes

- approximately **85%** of “preemies” with a very low birth weight **survive** to be discharged from the hospital within 2 years after discharge, **2 to 5%** die from medical complications related to their preterm birth.
- infants born at the **threshold of viability** (those with a gestational age of **23 to 25 weeks**, a birth weight of **less than 500 g**, or both) are at the greatest risk for a **poor outcome**.
- factors influencing **likelihood of survival**: 
  - gestational age
  - exposure to antenatal steroids
  - **female** sex
  - singleton gestation
  - higher **birth weight**
“Preemie”

- A child born at 22 weeks will almost certainly **die in the first 6 months**.
- A child born at 23 weeks **might survive** but will almost certainly be profoundly brain-damaged.
- A child born at 25 weeks has **~75% chance of making it to 6 months** and a better than 50/50 chance of not having brain gross brain damage on U/S.
- Even a preterm child born later is very likely to have serious disabilities as a result.

---

**End-of-life decisions in neonatal intensive care: physicians’ self-reported practices in seven European countries**
“Preemie”

Long-Term Outcomes

- A large proportion of extremely-low-birth-weight (ELBW) infants assessed in early childhood have motor, cognitive or neurosensory disability or cerebral palsy.
- Severe disability in early childhood generally persists at school age:
  - IQ of less than 85
  - Learning problems
  - Poor motor skills
  - Behavioral problems
- In adolescence or adulthood, ELBW “preemies” are more likely to have medical, functional or neurodevelopmental problems.
- However, many of those with a very low or extremely low birth weight were functional as young adults in terms of educational attainment, employment, and independent living, suggesting that early functional and cognitive impairments can be overcome.
Study suggests children born prematurely may face increased health risks into adulthood.

Association of Preterm Birth With Long-term Survival, Reproduction, and Next-Generation Preterm Birth
Geeta K. Swamy; Truls Østbye; Rolf Skjærvén

JAMA. 2008;299(12):1429-1436
Outcome with Respect to Overall Disability at 30 Months
Children Born at 22 through 25 Weeks of Gestation

- No disability (49%)
- Died (2%)
- No data (1%)
- Severe disability (23%)
- Other disability (25%)
**Germinal Matrix / Intraventricular Hemorrhage**
- < 30 weeks gestation
- due to high germinal matrix blood flow, high metabolic activity, "fragile" vessels, hypoxia with endothelial damage, increased venous pressure with poor autoregulation of cerebral blood vessels

**Necrotizing Enterocolitis**
- < 1500 g → bottle-fed → “immature” mucosa → ischemia → mucosal / full-thickness necrosis → pneumatosis intestinalis / pneumoperitoneum
- distal small bowel (“entero-”) and colon (“col-itis”)

**Hyaline Membrane Disease (HMD)**
(Respiratory Distress Syndrome (RDS) of the Newborn)
- “immature” type II pneumocytes → insufficient synthesis of surfactant
  - complex of surface-active phospholipids (mostly lecithin [dipalmitoylphosphatidylcholine])
- ↑ alveolar surface tension → alveolar collapse (atelectasis) → hypoxemia → vasoconstriction → hypoperfusion → endothelial damage + alveolar damage → hyaline membranes (fibrin + cell debris)
Necrotizing Enterocolitis (NEC)

- a syndrome of inflammation and necrosis of the small and large intestines

- develops in approximately 5 to 10% of very-low-birth-weight infants
- primarily affects infants who have received enteral feedings
- 15 to 30% of affected infants do not survive, and survivors have greater neurodevelopmental impairment than unaffected infants
- most infants have a response to medical management
  - bowel rest
  - systemic antibiotics
- 20 to 40% require surgery for bowel necrosis and perforation
- mortality among infants who require surgery is as high as 50% and is highest among the least mature infants
Necrotizing Enterocolitis (NEC)

- a serious gut problem in babies, especially bottle-fed “preemies”
- the etiology of NEC remains unclear (infectious) but prematurity is the most important risk factor for its development
  - “preemies” have a 100X increased risk for the development of NEC!!!
- inflammation and necrosis of the terminal ileum, cecum, and ascending colon produce a medical and surgical emergency
  - abdominal distention, ileus, bloody stools at several days of age
  - pneumatosis intestinalis
  - necrosis may become full-thickness → perforation!!!
one of the factors thought to contribute to this syndrome is **immaturity** of **gastrointestinal function**
- immature gastrointestinal motility
- digestive ability
- intestinal barrier function
- innate immunity

in addition, **commensal bacteria** in the gut may **modulate** the intestinal **inflammatory response**
- frequent treatment with **broad-spectrum antibiotics** and exposure to **nosocomial flora** modify bacterial colonization of the gut
- **abnormal bacterial colonization** after birth may induce a **hyperactive inflammatory response** to challenges to intestinal integrity and contribute to the development of NEC
NEC
Pathogenesis

Prematurity

Immaturity of intestinal:
- Motility and digestion
- Circulatory regulation
- Barrier function
- Immune defence

Hypoxic-ischaemic injury?

NEC

Abnormal bacterial colonisation

Feeding
a promising approach to the prevention of NEC is to **modify bacterial colonization of the gut**

- enteral administration of **“probiotic”** supplements (including lactobacilli, bifidobacteria, and saccharomyces)
- reduced the incidence and severity of necrotizing enterocolitis in small trials involving infants with very low birth weight

an alternative approach is the use of **“prebiotics”**

- nondigestible dietary supplements such as long-chain carbohydrates and mucins that promote intestinal growth of normal commensal organisms
- “prebiotics” given to preterm infants who are fed formula decrease colonization of the intestines with pathogenic bacteria
coagulative necrosis of mucosa

pneumatosis intestinalis of submucosa
mild mucosal necrosis

severe mucosal necrosis

transmural necrosis

pneumatosis intestinalis
Pneumatosis Intestinalis

(pneuma [Greek] wind, breath)
Necrotizing Enterocolitis (NEC)

- in 1 out of 10 LBW infants
- multifactorial
- associated with first feedings
  - ? bacterial introduction
- bloody stools
- terminal ileum, cecum, right colon
- eventually gangrene
- extremely poor prognosis!!!
NEC

- Serosa
- Submucosa
- Villus
- Circular muscle
- Longitudinal muscle
**mechanical ?**
- gas dissects into submucosa
- from lumen (through breaks in mucosa)
- from serosa ("tracking" along mesenteric blood vessels)
- but composition of gas is different than that of alveolar air!

**bacterial ?**
- gas-forming bacteria (e.g. *Clostridium perfringens*) get into submucosa through breaks in mucosa
- pneumatosis intestinalis may resolve following Abx therapy
- but cysts are sterile
- eventual pneumoperitoneum (after cyst rupture) follows a benign course (i.e. no peritonitis)

**biochemical ?**
- luminal bacteria produce excessive amounts of $\text{H}_2$ gas from fermentation of carbohydrates and other foodstuffs
- "pushed" directly into mucosa and then "trapped" in submucosa
- indeed, the $\text{H}_2$ content of cysts has been reported to be as high as 50%