NEONATOLOGY

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Genomics – Genetics

Dominant and recessive inheritance

X-bound inheritance

KNOWLEDGE
(Lysosomal storage diseases)

Chromosomal defects

Environmental conditions,
Multifactorial inheritance

Multiple developmental disorders

Diagnostics, therapy?
Introduction

- Significance of neonatology
- Basic terminology
- Diseases affecting the intrauterin life
  - Placenta
  - Diseases of the fetus
  - Diseases of the mother
- Diseases of the perinatal period

“Repetition makes the master” Developmental disorders and genetic diseases

Significance/1

- Diseases of neonates and infants:
  - Inherited disorders
  - Intrauterine effects
  - Maternal factors
  - Environmental factors

- Mortality in the below 1 year population is significantly greater than in the 1-24 year population

- Infant mortality is a quality measure of the health system:
  - Major branches of medicine are involved
  - International comparisons
Figure 1. Pedigrees of NSCH syndrome families, analysis of the claudin-1 gene structure, and protein expression. (A) Pedigrees of the NSCH families (wt, wild type; m, mutant). (B) Sequence showing the homozygous deletion in exon 1 (delT200-201) in patient V.3 compared with his heterozygous father (patient IV.2, pedigree 1) and the wildtype sequence (control), respectively. (C) Western blot analysis of claudin-1 using anti-claudin-1 polyclonal antibody (Zymed Laboratories) in confluent fibroblast culture of patients V.3 and V.5 (pedigrees 1) and liver of patient II.1 (pedigree 2); a ~23-kilodalton band corresponding to claudin-1 is present in controls but not in patient fibroblasts and liver. Actin is present in all samples. (D) Western blot analysis of claudin-2 using anti-claudin-2 polyclonal antibody in liver of patient II.1 (pedigree 2). Actin is used for loading control. A relative overexpression of claudin-2 is observed in patient II.1 liver.

Figure 2. Sclerosing cholangitis with neonatal onset: cholangiogram, liver histology, and claudin expression. (A) Operative cholangiogram (patient II.1) shows the patency of the extrahepatic bile ducts but abnormalities in the intrahepatic bile ducts. Note the network of thin irregular intrahepatic channels. (B) Surgical liver biopsy specimen (patient V.5), absence of interlobular bile duct, numerous arterial branches. (C) Skin of patient V.4 showing lack of claudin-1 in epidermis whether (D) claudin-4 is present in the granular layer. (E and F) Normal localization of claudin-1 in cholangiocytes and hepatocytes in unaffected human liver. (G) Liver of patient V.5 showing lack of claudin-1 but background fluorescence caused by cholestatic liver cell injury (there was no bile duct in the biopsy specimen). (H) whether claudin-2 is present at the hepatocyte membranes.
Significance/2

• Pregnancy outcomes:
  – Normal healthy baby
  – Adverse pregnancy outcome
    • Death of a foetus/infant
    • Growth restriction, prematurity, overgrowth
    • Congenital anomalies

• Questions
  – Why did it happened?
  – Will it happen again?
  – (Any risk to the family?)

People involved in pregnancy care

• Classic model:
  – Obstetrician
  – Midwife

• Modern approach:
  – Midwife
  – Obstetrician – Foetomaternal Medicine consultant
  – Paediatrician – Neonatologist
  – Geneticist, Cytogeneticist
  – Pathologist – Perinatal pathologist
Pregnancy care

• First visit (booking):
  – Pregnancy test
  – Blood tests: blood group, haemoglobin, infective agents (rubella, CMV, toxoplasma, syphilis, HIV)
  – Urine test (glucose, protein)
  – Blood pressure
  – Dating scan

• 16th week
  – Triple test: serum AFP, hCG, unconjugated oestriol
  – Nuchal translucency scan

• 18-22nd weeks
  – Anomaly scan
Pregnancy care

- Third trimester:
  - Regular checkups:
    - Foetal heartbeat doppler monitoring
    - Abdominal examination
      - Baby position
      - Fundal height
    - CTG
  - Preeclampsia screen
    - Blood
    - Urine
    - Blood pressure

DEVELOPMENT 0-56 days (2 months)
CAUSES OF INTRAUTERINE DEATH

- 25-60% not identified (Fretts 2015, Uptodate)
- Cunningham (2010, Williams Obstetrics)
  - Fetal 25-40%
  - Placental 25-30%
  - Maternal 5-10%
  - No reasonable explanation 15-35%

Maternal causes of intrauterine death (15)

- Diabetes
- Hypertonia
- Obesity
- Age >35 years
- Thyroid disease
- Kidney disease
- Antiphospholipid antibodies
- Thrombophilia
- Smoking
- Drugs and alcohol
- Infections, sepsis
- Premature birth
- Peculiar uterine contractions, pains
- Uteral rupture
- Overcarrying of the pregnancy
Fetal diseases and intrauterine death or death at birth

- Major malformations 15-20%
- Feto-maternal bleeding 5%
- Hydrops fetalis
- Fetal arrhythmia
- Alloimmune thrombocytopenia (stroke)
- Rh isoimmunisation

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**Early miscarriage – first trimester**

- Loss of pregnancy up the 20th week of gestation
- Frequency:
  - 65-80% of very early pregnancies and 15-25% of recognised pregnancies are aborted in the first and second trimesters
- Cause:
  - Up to 80% chromosomal
    - Trisomies
    - Polyploidy
    - Sex chromosome monosomy
  - Increased risk:
    - Maternal age
Incidence of chromosomal abnormalities

![Graph showing incidence of chromosomal abnormalities vs maternal age]

- **Maternal age**
- **Down syndrome**
- **All chromosomal aberrations**

Late miscarriage

- **Second trimester, up to the 24th week**
- **Frequent malformations seen:**
  - **Neural tube defects:**
    - anencephaly, encephalocele, myelomeningocele
  - **Amnion rupture sequence**
    - Amnion bands, disruptions, deformations
  - **Cystic hygroma**
  - **Omphalocele**
  - **Renal malformations, urethra obstruction**
  - **Cardiac abnormalities**
- **The cause is usually unknown – congenital malformations are not sufficient!**
Diagnosis of the developmental disorders

- **Prenatal Diagnostics - Prevention**
  - Ultrasonography, AFP, analysis of blood of the mother (non-invasive Methods)
  - Definitive genetic diagnosis (invasive Methods)
    - Amniocentesis
    - Chorion biopsy
    - Embryo Skin biopsy

- **Necessary to perform:**
  - older mother
  - parents are carrier of diseased genes or chromosomes
  - previous pregnancy with malformations
Mid-gestation ultrasound scan

- Becoming a standard procedure, between 18\textsuperscript{th} and 22\textsuperscript{nd} weeks
  - Foetal biometry
  - Genetic screening ("anomaly scan"):  
    - Neural tube defects
    - Skeletal dysplasias
    - Abdominal wall defects
    - Hydrocephalus
    - Duodenal atresia
    - Foetal hydrops
    - Facial clefts
    - Cardiac abnormalities
  - Placental implantation site
  - Identifying multiple gestation
### Sensitivity of the anomaly scan

<table>
<thead>
<tr>
<th></th>
<th>Routine scan</th>
<th>Anomaly scan</th>
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<tbody>
<tr>
<td>0%</td>
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<tr>
<td>20%</td>
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<tr>
<td>40%</td>
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<td></td>
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<tr>
<td>60%</td>
<td></td>
<td></td>
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<tr>
<td>80%</td>
<td></td>
<td></td>
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<tr>
<td>100%</td>
<td></td>
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</tbody>
</table>

- **Anencephaly**
- **Spina bifida**
- **Severe cardiac defect**
- **Diaphragmatic hernia**
- **Gastroschisis**
- **Exomphalos**
- **Renal anomalies**

### Results of the anomaly scan

- **Normal foetal development, no detectable anomaly**
- **Significant malformation:**
  - Severe cardiac defect
  - Neural tube defect
  - Amnion band sequence
  - Termination of pregnancy
- **Non-lethal malformation**
  - May be part of a single gene disorder, chromosomal defect or sequence!
  - Short femur, exomphalos, gastroschisis, facial clefts

  - Further testing – amniocentesis (12 weeks), chorion villous biopsy (18-20 weeks), genetic referral
Amnion band sequence
Results of the anomaly scan

• Result of unknown significance (soft marker)
  – Isolated change, may be associated with major malformations in a fraction of cases
  – Soft markers:
    • Isolated cerebral ventriculomegaly
    • Isolated echogenic bowel
    • Isolated choroid plexus cyst
    • Isolated pyelectasis
    • Single umbilical artery
    • Nuchal fold thickness and echogenity
    • Cystic hygroma
  – Further testing, genetic referral!
The viable foetus

- From 24 weeks to birth
- Protected position
- Factors influencing foetal growth:
  - Nutrition, oxigenation, potential to develop
  - Foeto-materno-placental unit
    - Foetal disorders
    - Maternal factors
      - Diseases
      - Social factors
    - Placenta
  - Environmental factors
Causes of intrauterine stress

- **Uterus and placenta**
  - Decreased perfusion
  - Placental abruption
  - Placenta previa
  - Placental inflammation

- **Foetal**
  - Multiple gestation
  - Foetal infection
  - Inherited disorders
  - Blood group dyscrasias, foetal hydrops

- **Maternal**
  - High blood pressure
  - Chronic renal failure
  - Diabetes
  - Cardiovascular or respiratory insufficiency
  - Inadequate nutrition, anaemia
  - Infection
  - Alcohol, drugs, medication
  - Smoking

PIH, PET, HELLP

- 2-8% of pregnancies
- Major cause of maternal deaths
  - (England 15%, Columbia 50%)
- Forms:
  - Pregnancy induced hypertension (PIH)
  - Pre-eclampsia – toxaemia (PET)
  - Haemolytic anaemia, elevated liver enzymes, low platelet (HELLP)
- Aetiology:
  - Failed remodelling of the decidual vessels
- Treatment and prevention
  - Magnesium
Maternal diabetes

- Frequency: 2.5/1000 livebirths
- Maternal presentation:
  - Known diabetic
  - Impaired glucose tolerance (IGT)
  - Gestational diabetes
- Foetal complications:
  - Macrosomia – shoulder dystocia at birth
  - Hypoglycaemia of the newborn
  - Malformations:
    - Cardiac
    - Sacrum and lower limb

Foetal alcohol syndrome

- The most common preventable foetopathy
  - 1.9/1000 livebirths
- Characteristic facial features
- Intrauterine growth restriction
- Slow mental development, mental retardation
- Restlessness, hyperactivity
- Cardiac abnormalities: ASD, VSD
- Limb deformities
**Hydrops**

- Generalized oedema of foetus and placenta
- Can be associated with a cystic hygroma
- Causes:
  - Transplacental infection
    - Parvovirus B19, CMV
  - Inherited haemoglobinopathies
    - Thalassaemia
  - Blood group dyscrasias
    - Rh factor incompatibility
  - Chromosomal anomalies
    - Turner syndrome, Down syndrome

**Consequences of intrauterine stress**

- Chronic stress:
  - Low birthweight
    - SGA/IUGR
  - Prematurity
  - Stillbirth
- Acute stress:
  - Meconium release
  - Hypoxic haemorrhages
  - Foetal death, stillbirth
  - Prematurity
Stillbirths according to gestational age

ONS-US data, 2002

![Graph showing stillbirths according to gestational age]

Cases/year


- All cases
- Asphyxia, anoxia
- Congenital disorders

[Image of a baby's brain with text: '5mm 1:2']
The ‘disposable organ’

- Functions of the placenta:
  - Hormone synthesis – hCG, hPL/hCS, hCT, hCACTH, progesterone, oestrogen, relaxin
  - Immune barrier
    - Protecting the immunologically ‘foreign’ foetus from the maternal immune system
  - Mostly substitutes the functions of the foetal lungs, kidneys, intestines, liver
    - Gas exchange
    - Exchange of nutrients and waste

- (Functions of the foetal organs:
  - Lungs and intestines: maturation
  - Kidneys: production of amniotic fluid
  (oligohydramnion, polyhydramnion (CAVE: CMV !)
  - Liver: haematopoesis)

Weight development of foetus and placenta

Stocker: Paediatric pathology
I. Placenta

- Structure
  - Maturation disorders
  - Implantation disorders
  - Circulation
  - Inflammation
  - Proliferative changes (gestation trophoblast diseases)

- Placenta insufficiency
## Development of Placenta:

<table>
<thead>
<tr>
<th>Primary villus</th>
<th>Secondary villus</th>
<th>Tertiary villus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroma rich</td>
<td>Vessel are central</td>
<td>Scanty of stroma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sinusoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syntitio le capillaris membrane</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Big surface ratio</td>
</tr>
</tbody>
</table>
Placenta pathology I.

- Maturity disorders
  - **Late maturity**: Sinusoids are not or lately developed
  - **Early maturity**: Early ageing of placenta, might cause intrauterine retardation of the fetus
Maturity disorders

• Dysmaturity
  – Not specific, should not be evaluated alone
  – Major known reasons:
    • Maternal diabetes
    • Genetic disorders
  – Signs indicating chromosome-disorders
    • Formal disorders of the villus
    • Villus edema
    • Trophoblast mineralization
Toxoplasma placentitis

Acute placenta insufficiency.

• Cause:
  – Maternal circulatory shock
  – Large placenta infarction
  – Retroplacental haematoma

• Result:
  – Acute fetal hypoxia
  – Petechial haemorrhages
  – Brain oedema
  – Intrauterine death
Subacute placenta insufficiency.

• Cause:
  – Maternal cardial or respiratory insufficiency
  – Multiplex small placenta infarction
  – Inflammations
  – Placenta developmental disorders

• Result:
  – Intrauterine death
  – Premature birth
  – Intrauterine retardation

Chronic placenta insufficiency.

• Cause:
  – Inadequate nutrition
  – Placentitis
  – EPH gestosis

(Gestosis: pregnancy induced hypertensive states, including EPH gestosis when Edema and Proteinuria accompany Hypertension; other hypertensive disorders that develop during pregnancy or the puerperium are preeclampsia and eclampsia, either of which may be superimposed upon chronic hypertensive vascular or renal disease.

• Result:
  – Intrauterine retardation
**Eclampsia:** Fits (seizures) from severe high blood pressure in pregnant women.

**Eclampsia:** convulsions and coma occurring in pregnant or puerperal women, associated with Edema („weight gain“) and Proteinuria (Urine laboratory check) and Hypertension (physical examination – screening) (EPH).

**Eclampsia:** a toxic condition characterized by convulsions and possibly coma during or immediately after pregnancy.

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**Pathology of the umbilical cord**

- **Mechanical trauma:**
  - knots, pseudoknots, torsion, rupture

- **Rupture caused by placenta praevia**

- **Vascular anomalies:**
  - Vessel thrombosis
  - Aneurysm, rupture
  - One umbilical artery: sign of fetal malformations

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![Pathology of the umbilical cord](image)
Dysruptions

- Development of deformity because of total or partial damage of one organ after full development of the organs

- Reason:
  - compressed by amniotic band
  - intrauterine closure of a vessel and following infarction
  - atresies, porencephaly
multiple developmental disorders

- two or several organ systems are involved, the ethiology of the damage is the same

- Reason:
  - Infection (TORCH complex, varicella)
  - Chemicals
  - Aberration of chromosomes
  - e.g.: rubella (German measles) syndrom, fetal alcohol (consumption) syndrom, thalidomide (Contergan)

ZIKA VIRUS
Pathology of the placenta - difficulties

- Many changes in the placenta do not correlate well with the pathology of the foetus
- The significant changes are now being recognised
- Major abnormalities:
  - Disorders of maturation
  - Disorders of implantation
  - Circulatory disorders
  - Inflammation
  - Tumours
  - Umbilical cord abnormalities
Inflammation

• Acute chorioamnionitis
  – Ascending genital tract infection
  – Outcome:
    • Foetal death
    • Prematurity
    • Congenital infection – foetal pneumonia
  – IRDS

• Chronic villitis/intervillositis
  – TORCH complex, VUO
  – (villitis of unknown origin)
  – Outcome:
    • Early infection – teratogenicity
    • Late infection:
      – Foetal death
      – Hydrops (eg. Parvovirus B19)
      – Asymmetric intrauterine growth restriction (IUGR)

Premature rupture of membranes (PROM) is a spontaneous break or tear in the amniochorial sac before onset of regular contractions, resulting in progressive cervical dilation. Labor usually starts within 24 hours; more than 80% of these neonates are mature. The latent period (between membrane rupture and onset of labor) is generally brief when the membranes rupture near term; when the neonate is premature, this period is prolonged, which increases the risk of mortality from maternal infection (amnionitis, endometritis), fetal infection (pneumonia, septicemia), and prematurity.

Inflammation

• Acute chorioamnionitis
  – Ascending infection – genital tract/direct contamination, rupture
    – Early amniotic rupture
    – death
    – Premature birth
    – Congenital infection – pneumonia - IRDS

• Chronic villitis/intervillositis
  – TORCH complex/VUO (villitis of unknown origin)

  • Early infection – teratogenicity
  • Later infection:
    - death
    – Hydrops (pl. Parvovirus B19)
    – Asymmetric developmental disorder (IUGR)
Acute chorioamnionitis

• Simple diagnosis?

  – Often misdiagnosed!
    • Mixing up the terms: Membranitis – chorioamnionitis
    • Disregarding compartments of inflammation:
      • - Maternal inflammatory response
        - Fetal inflammatory response
    • Neglecting severity and importance of inflammation!

Compartments of Inflammation

• Fetal membranes
  – Maternal inflammatory response
  – Reaction of detachment of the placenta

• Umbilical cord
  – Fetal inflammatory response

• Chorion sheet
  - Maternal inflammatory response
  - Fetal inflammatory response
Acute chorioamnionitis vs membranitis
Maternal and Fetal inflammation
Maternal and Fetal Inflammation

Maternal Inflammation
Foetal inflammation – early thrombus
Disorders of implantation

- Depth of implantation:
  - Placenta accreta, percreta, increta
  - Uncontrollable haemorrhage when shedding of the placenta

- Place of implantation:
  - Placenta praevia
    - Implantation site over the internal os of the cervix
    - Placental rupture and abruption during labour

Circulatory disorders

- Foetal vessels:
  - Villous artery thrombosis – inherited coagulopathies
  - Villous damage – loss of foetal blood into maternal circulation

- Maternal vessels – uterine and decidual vessels
  - Infarcts (location, extent)
  - Clots, haemorrhages
  - Intervillous thrombi
  - Placental abruption
  - Subchorionic haematoma
Umbilical cord abnormalities

- 60 cm average (45-75cm)
  - Too long cord:
    - Cord prolapse
    - Cord around neck (suffocation)
    - True knots
  - Too short cord: tension \( \uparrow \), \( \rightarrow \) hypoxia
    - Placental abruption
    - Uterus inversion
- 1 twist/5cm average
  - Overcoiled/undercoiled cord – increased incidence of stillbirth

Insertion:
- Central, lateral, marginal
- Velamentous

Multiple gestation

- Frequency: 10-20/1000 pregnancies
- More common:
  - Family history of twinning
  - Infertility problems
    - Induced ovulation
    - IVF
- Forms:
  - Monoamniotic monochorionic
  - Diamniotic monochorionic
  - Diamniotic dichorionic
MONOZYGOTIC TWINS
- FERTILIZED OVUM
- TWO CELLS
- TWO MORULAS
- ONE MORULA
- EMBRYONIC DISK DIVISION
- CHORION
- AMNIONIC CAVITY
- DIAMNIONIC DICHRORIONIC
  - 8% OF ALL TWINS
- DIAMNIONIC MONOCHORIONIC
  - 20% OF ALL TWINS
- MONOAMNIONIC MONOCHORIONIC
  - <1% OF ALL TWINS

DIZYGOTIC TWINS
- TWO FERTILIZED OVA
- IMPLANTATION SEPARATELY
- UTHERUS
- IMPLANTATION TOGETHER
- DIAMNIONIC DICHRORIONIC
  - 72% OF ALL TWINS

---

250 Obladen, History of twin reversed perfusion

Figure 2 (A) Hydroptic acardius aneup “larger and heavier than the accompanying twin”, described by Kühler 1777 [16]. (B) acardius acardius with twisted cord depicted by Althoff 1882 to “illustrate the connection of the acardius with his twin brother and the placenta” [J].
Dangers of twinning

• Conjoined twins
  – Symmetric
    • Craniopagus
    • Thoracopagus
    • Pygopagus
  – Asymmetric
    • Acardius amorphus
Amnion cavities

Separating membrane

Vascular distribution

60%

40%

Vascular equator
Anastomoses

Vascular distribution

20%  80%
Anastomosis-types

- Monoamniotic monochorial:
  - Arterio-arterial
  - Veno-venous
- Two way flow is possible

- Diamniotic monochorial:
  - Arterio-venous
- Only one way flow is possible
Dangers of twinning

- Premature birth
- Low birth weight
- Twin to twin transfusion (TTTS)
  - Arteriovenous vascular connection in the placenta between the two fetal circulations
  - Greatest chance of TTTS in diamniotic monochorionic gestation
The process of birth

• First phase:
  – Foetus positioned into the birth canal
    • Abnormal presentation, size discrepancies

• Second phase
  – Pushing
    • Asphyxia and trauma, ineffective contractions, prolonged pushing, instrumental extraction, cord compression, meconium aspiration

• Third phase
  – Birth of the placenta
    • Haemorrhagic complications

The newborn

• Weeks of gestation
• Mode of birth: (cesarean section, extraction)
• Birthweight
• Apgar score (0-10 pts.)
  – Cardiac frequency
  – Breathing
  – Muscle tone
  – Pharynx reflex
  – Skin colour
Birth trauma, Intrapartum complications

Fractures:
Clavicle, long bones, cranial fracture (instrumental extraction)
Arm paresis (manual extraction)

Haemorrhages:
Scalp haemorrhage (vacuum extraction), subgaleal, subdural hematoma, intraspinal,
• Vertebral column haemorrhage

Visceral haemorrhages (eg. adrenal)

Intrapartum death:
Asphyxia during the second stage

Conditions affecting the newborn

Placental disorders
• Amniotic fluid infection
• Abruptio placenta
• Premature rupture of membranes
• Large placenta infarcts
• Intervillous thrombosis
• Umbilical cord compression, knots
• Placenta growth retardation
• Placenta praevia
• Marginal sinus rupture

Fetal disorders
• Congenital anomalies
• Blood group dyscrasia
• Birth trauma
• Polyhydramnion
• Caesarean section
• Prematurity
• Postmaturity
• Congenital syphilis
The neonate

- From birth to the 28th day
  - (Perinatal age 0-7 days)
- Birthweight
  - Low birthweight
    - Prematurity = weight consistent with gestational age
    - SGA/IUGR = weight lower than the 10th centile
  - Large birth weight:
    - Diabetes,
    - overdue gestation,
    - (syndromes)
- Apgar score (0-10 pont)
  - Cardiac frequency
  - Breathing
  - Muscle tone
  - Reflex (pharynx)
  - Skin colour

Low birth weight: Two groups of neonates are born weighing less than the normal minimum birth weight of 2,500 g (5½ lb)—those who are born prematurely (before the 37th week of gestation) and those who are small for gestational age (SGA). The premature neonate weighs an appropriate amount for his gestational age and probably would have matured normally if carried to term. Conversely, the SGA neonate weighs less than the normal amount for his age; however, his organs are mature. Differentiating between the two groups, helps direct the search for a cause.

Mortality according to birth weight

<table>
<thead>
<tr>
<th>Weight g</th>
<th>Mortality %</th>
</tr>
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<tbody>
<tr>
<td>0-999</td>
<td>100</td>
</tr>
<tr>
<td>1000-1499</td>
<td>100</td>
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<tr>
<td>1500-1999</td>
<td>100</td>
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<tr>
<td>2000-2499</td>
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<tr>
<td>2500-2999</td>
<td>100</td>
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<tr>
<td>3000-3499</td>
<td>100</td>
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<tr>
<td>3500-3999</td>
<td>100</td>
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<tr>
<td>4000-4499</td>
<td>100</td>
</tr>
<tr>
<td>4500-5000</td>
<td>100</td>
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</table>
Because low birth weight may be associated with poorly developed body systems, particularly the respiratory system, your priority is to monitor the neonate’s respiratory status. **Be alert for signs of distress, such as apnea, grunting respirations, intercostal or xiphoid retractions, or a respiratory rate exceeding 60 breaths/minute after the first hour of life.** If you detect any of these signs, prepare to provide respiratory support. Endotracheal intubation or supplemental oxygen with an oxygen hood may be needed.

**Monitor the neonate’s axillary temperature.** Decreased fat reserves may keep him from maintaining normal body temperature, and a drop below 97.8°F (36.5°C) exacerbates respiratory distress by increasing oxygen consumption. To maintain normal body temperature, use an overbed warmer or an Isolette. (If these are unavailable, use a wrapped rubber bottle filled with warm water, but be careful to avoid hyperthermia.) Cover neonate’s head to prevent heat loss.
Causes of perinatal deaths

2nd Dept. Of Pathology data 1998-2000

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Immaturity</td>
<td>29%</td>
</tr>
<tr>
<td>Malformation</td>
<td>26%</td>
</tr>
<tr>
<td>Placental disorder</td>
<td>15%</td>
</tr>
<tr>
<td>Peripartum complication</td>
<td>9%</td>
</tr>
<tr>
<td>Infection</td>
<td>4%</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>17%</td>
</tr>
</tbody>
</table>

The premature neonate

- Low birth weight
- Low Apgar score
- Immaturity:
  - Lungs
  - CNS
- Treatment
  - Agressive oxigen therapy
  - Catheters
  - Complications
Heart

- Congenital heart disease (CHD) occurs in 1/125 live births.
- Neonates may present with a variety of non-specific findings, including:
  - tachypnea
  - cyanosis
  - pallor
  - lethargy
  - FTT
  - sweating with feeds
- More specific findings include:
  - pathological murmurs
  - hypertension
  - abnormal pulses
  - syncope

**FTT:** Failure to thrive (FTT) refers to a baby or child that is not developing as well as desired.
The first question when considering FTT is whether there is actually anything wrong. Slowed weight gain (but not weight loss) in an infant could be part of the normal growth curve for this individual infant, or could merely indicate minor changes such as a more active baby.
On the other hand, failure to thrive can have serious causes, and it is prudent to monitor weight, height, and other statistics. If there is something wrong, then it can range from minor breastfeeding pattern problems, to extremely serious metabolic and major organ disorders.

Congenital Heart Disease

- Neonates with CHD often rely on a patent ductus arteriosus and/or foramen ovale to sustain life.
- Unfortunately for these neonates, both of these passages begins to close following birth.
  - The ductus normally closes by 72hrs.
  - The foramen ovale normally closes by 3 months.
CHD

- In the presence of hypoxia or acidosis (generally present in ductus-dependent lesions), the ductus may remain open for a longer period of time.
- As a result, these patients often present to the ED during the first 1-3 weeks of life.
  - i.e. as the ductus begins to close.

Classifying CHD

- There are many different classification systems for CHD.
  - None are particularly good.
- I will be discussing the Pink/Blue/Grey-Baby system:
  1. **Pink Baby** – Left to right shunt
  2. **Blue Baby** – Right to left shunt
  3. **Grey Baby** – LV outflow tract obstruction

LUNG - Diseases of the premature neonate

- **Respiratory:**
  - **IRDS** (idiopathic respiratory distress syndrome), hyaline membrane disease
  - **BPD** (bronchopulmonary dysplasia)
  - Interstitial emphysema, pneumothorax
  - Pulmonary haemorrhage
  - Pneumonia, sepsis
RDS

- Respiratory Distress Syndrome
- Immaturity of Lungs
- Need Surfactant
- Need Ventilation

Reticugranular
(Ground Glass)
Air Bronchogram
Diseases of the premature neonate

- Central nervous system:
  - Intraventricular haemorrhage (IVH)
  - Internal hydrocephalus
  - Kernicterus
- Intestinal:
  - Necrotizing enterocolitis (NEC)
Diseases of the premature neonate

- **Ocular**
  - Retinopathy of prematures (ROP), retroental fibroplasia

- **Infection**
  - Intrauterine contamination
  - Immature immune system
  - Iatrogenic infections

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Neonatal and infant mortality

**CESDI data**

<table>
<thead>
<tr>
<th>Category</th>
<th>Neonatal Mortality</th>
<th>Infant Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immaturity</td>
<td>12.5%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Congenital defect</td>
<td>27.4%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Intrapartum complication</td>
<td>1.4%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Infection</td>
<td>15.9%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Sudden infant death</td>
<td>30.1%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Accident/trauma</td>
<td>3.8%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other</td>
<td>8.0%</td>
<td>8.0%</td>
</tr>
</tbody>
</table>

60% 0% 60%
Investigation of SUDI

- Sudden death of a previously healthy infant
- Causes: - ?
  - Immature CNS respiratory centers
  - Latent cardiac conductance defect
  - Trigger event – eg. Infection
- Natural or unnatural death?
  - Legal consequences – the parents/carers are under suspicion during the investigation
- Asymptomatic disorders
  - Some congenital heart defects, metabolic catastrophes, infectious disorders
  - Abuse
    - Shaken baby syndrome
    - Münchausen syndrome by proxy
- Cases of mistakenly prosecuted parents

Causes of SUDI
Scandinavia 1990-2000

- SIDS: 56%
- Other unknown SUDI: 9%
- Disease: 22%
- Accident/trauma: 7%
- Neglect: 2%
- Abuse: 2%
- Homicide: 2%
SIDS risk factors

- **Sociodemographic factors:**
  - Family circumstances
  - Male infant
  - Winter period

- **Pregnancy history**
  - Multiparous mother
  - Low birth weight
  - Smoker mother, father
  - Maternal cocaine, opiate abuse
  - Alcohol abuser mother

- **Factors after birth:**
  - Infections
  - Passive smoking
  - Sleep position – prone or side
  - Bed-sharing
  - Soft sleep surface
  - Covering of head
  - Overheating

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**SIDS incidence per thousand**
Prevention

- „Back to sleep”
- Sleep surface
- No bedsharing
- Covers, duvets, clothing
- Ambient temperature

CHD- Pink Baby (L → R shunt)

- L → R shunts cause chronic heart failure (CHF-congenital heart failure) and pulmonary hypertension.
- This leads to RV enlargement, RV failure, and cor pulmonale.
- These babies present with CHF and respiratory distress.
  - They are not typically cyanotic.
Pink Baby (L → R shunt)

- These lesions include (among others) ASD’s, VSD’s, and persistently patent ductus arteriosus.
Pink Baby (L → R shunt)

• Diagnosing L → R shunts depends on:

  1. Examination findings:
     • Non-cyanotic infant in resp distress.
     • Crackles, widely-fixed second heart sound, elevated JVP, cor pulmonale.

  2. RTG:
     • Increased pulmonary vasculature (suggestive of CHF).
     • RA and/or RV enlargement.

  3. ECG:
     • RAE and/or RVH.

Pink Baby (L → R shunt)

• Initial management should be directed at reducing the pulm edema.

Cardiologist should be consulted urgently regarding use of:

  – Morphine
  – Nitrates
  – Digoxin
  – Inotropes
Blue Baby (R → L shunt)

- R → L shunts cause hypoxia and central cyanosis.
- Neither hypoxia or cyanosis tend to improve with 100% oxygen.
- R → L lesions include (among others):
  - Tetralogy of Fallot (TOF)
  - Transposition of the Great Arteries (TGA)

Tetralogy of Fallot

1. Pulmonary OTO (outflow tract obstruction: valve or trunc)
2. RV hypertrophy
3. VSD
4. Over-riding aorta
   - With severe pulmonary OTO...

bloodflow to the lungs may be highly ductus-dependent.
Tetralogy of Fallot

- The classic X-Ray finding in TOF is the boot-shaped heart.

- Pulmonary vasculature is typically decreased.

Transposition of the Great Arteries

- TGA is the most common cyanotic lesion presenting in the first week of life.

- Anatomically:
  - RV → aorta
  - LV → pulmonary aa

- To be compatible with life, mixing of the two circulations must occur via an ASD, VSD, or PDA.
Transposition of the Great Arteries

- The CXR (chest X-Ray) findings in TGA are typically less dramatic than in TOF.
- Pulmonary vasculature is typically increased.

Blue Baby (R → L shunt)

- Hypoxia and cyanosis (unresponsive to oxygen) in the neonatal period suggests a ductus-dependent lesion.
- Treatment is a prostaglandin-E1 (PGE₁) infusion.
  - Dosing discussed momentarily
- This should obviously be accompanied by urgent pediatric cardiology examination and consultation.
Grey Baby (LVOTO)

• Left-ventricular outflow tract obstructions (LVOTO’s) lead to cyanosis, acidosis, and shock early in the neonatal period.

• Complete obstruction is universally fatal unless shunting occurs through an ASD, VSD, or PDA.

• Examples of these lesions include:
  – Severe coarctation of the aorta
  – Hypoplastic left heart syndrome (HLHS)

Grey Baby (LVOTO)

• Treatment:
  – Any neonate presenting with shock unresponsive to fluids +/- pressors has a LVOTO until proven otherwise.
  – As with the Blue babies, appropriate management is an urgent PGE1 infusion and emergent consultation.
Prostaglandin-E₁

- PGE₁ promotes ductus arteriosus patency.
- Use an IV infusion at 0.05-0.1 ug/kg/min.
- A response should be seen within 15 min.
  - If ineffective, try doubling the dose.
  - If effective, try halving the dose.
- The lowest possible dose should be used—adverse-effects of PGE₁ can include:
  - fever
  - flushing
  - diarrhea
  - periodic apnea
  (be ready to intubate)