NEONATOLOGY

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Genomics – Genetics

Dominant and recessiv inheritance

X-bound inheritance

KNOWLEDGE
(Lysosomal storage diseases)

Chromosomal defects

Environmental conditions,
Multifactorial inheritance

Multiple developmental
disorders

Diagnostics, therapy ?

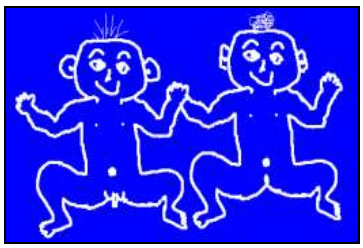
Introduction

- 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

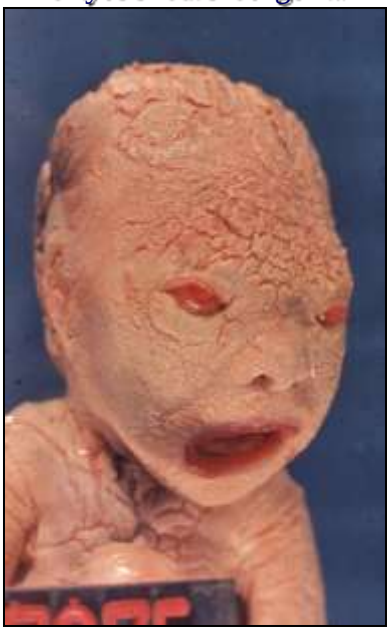
- Diseases of neonates and infants:
  - Inherited disorders
  - Intrauterine effects
  - Maternal factors
  - Environmental factors



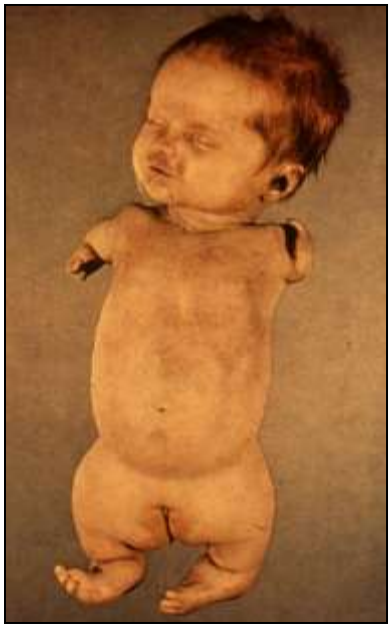
- Mortality in the below 1 year population is significantly greater than in the 1-24 year population

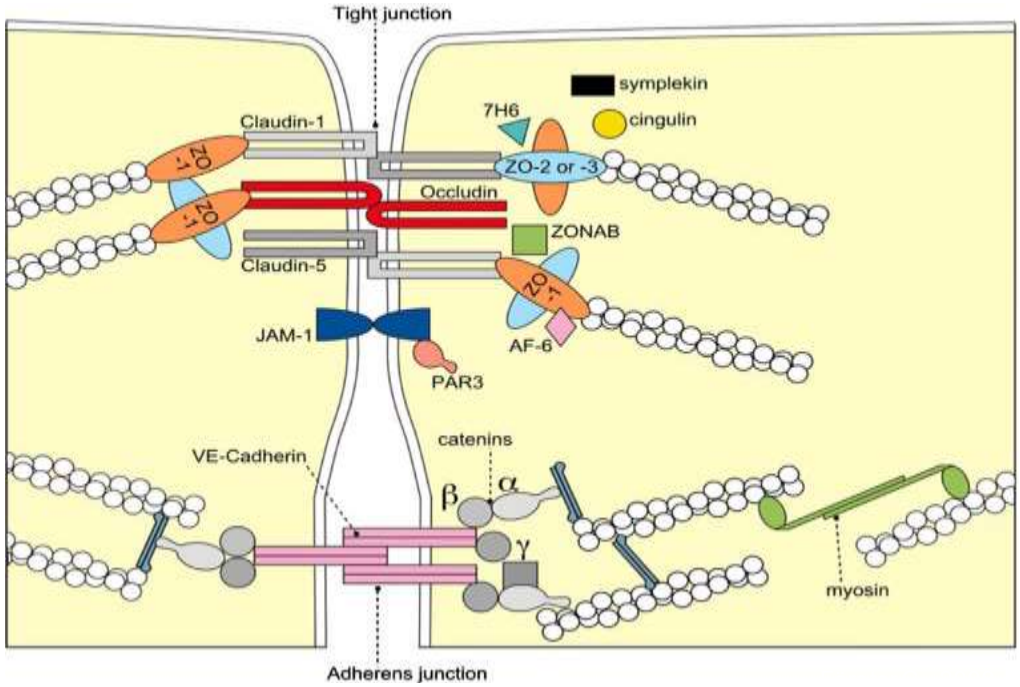
- Infant mortality is a quality measure of the health system:
  - Major branches of medicine are involved
  - International comparisons

Ichtyosis cutis congenita



Phocomelia





GASTROENTEROLOGY 2004;127:1388–1398

Claudin-1 Gene Mutations in Neonatal Sclerosing Cholangitis Associated With Ichthyosis: A Tight Junction Disease

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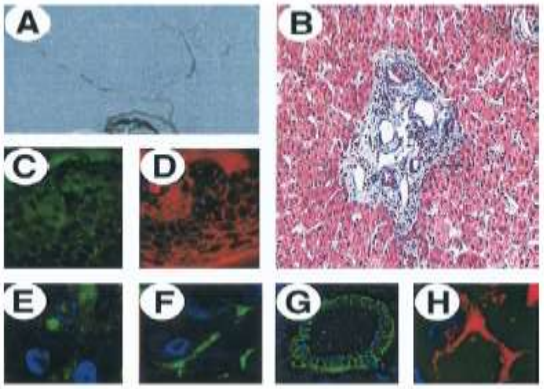


Figure 2. Sclerosing cholangitis with neonatal onset: cholangiogram, liver histology, and claudin expression. (*A*) Operative cholangiogram (patient II-1) shows the patency of the extrahepatic bile ducts but abnormalities in the intrahepatic bile ducts. Note the network of thin irregular intrahepatic 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.

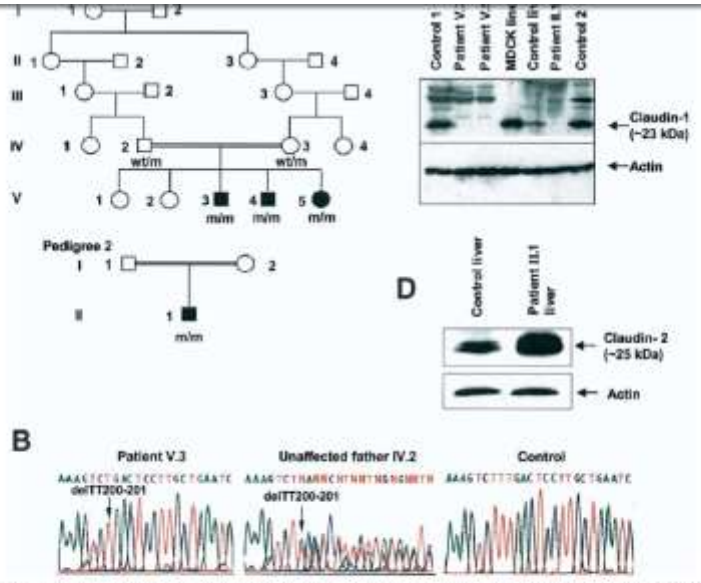


Figure 1. Pedigrees of NISCH syndrome families, analysis of the claudin-1 gene structure, and protein expression. (*A*) Pedigrees of the NISCH families (wt, wild type; m, mutant). (*B*) Sequence showing the homozygous deletion in exon 1 (delTT200–201) in patient V.3 compared with his heterozygous father (patient IV.2, pedigree 1) and the wild-type 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 (pedigree 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.

Significance/2

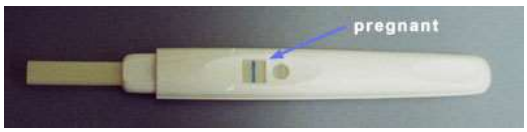
- Pregnancy outcomes:
  - Normal healthy baby
  - Adverse pregnancy outcome
    - Death of a foetus/infant
    - Growth restriction, prematurity, overgrowth
    - Congenital anomalies
- Questions
  - Why did it happened?
  - Will it happen again?
  - (Any risk to the family?)

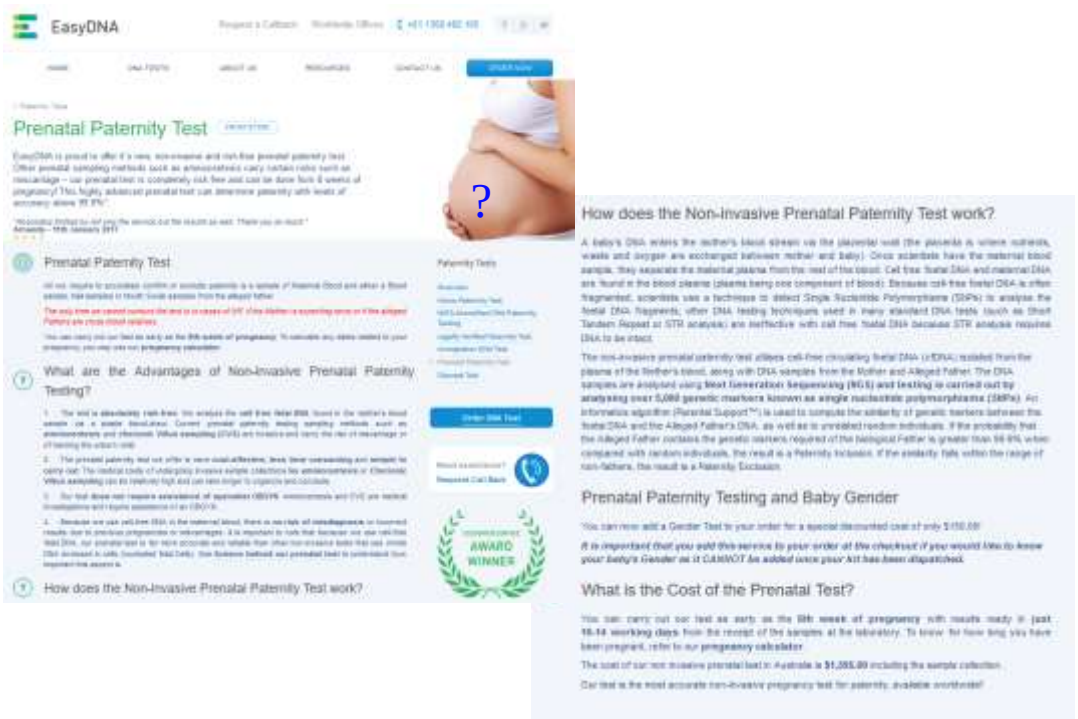
People involved in pregnancy care

- Classic model:
  - Obstetrician
  - Midwife
- Modern approach:
  - Midwife
  - Obstetrician – Foetomaternal Medicine consultant
  - Paediatrician – Neonatologist
  - Geneticist, Cytogeneticist
  - Pathologist – Perinatal pathologist

Pregnancy care

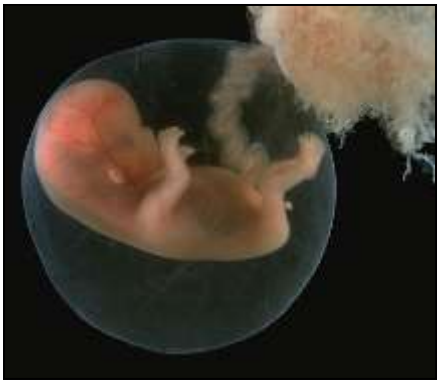
- First visit (booking):
  - Pregnancy test
  - Blood tests: blood group, haemoglobin, infective agents (rubella, CMV, toxoplasma, syphilis, HIV)
  - Urine test (glucose, protein)
  - Blood pressure
  - Dating scan
- 16th week
  - Triple test: serum AFP, hCG, unconjugated oestriol
  - Nuchal translucency 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



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*
- *Kideny disease*
- *Antiphospholipid antibodies*
- *Thrombophilia*

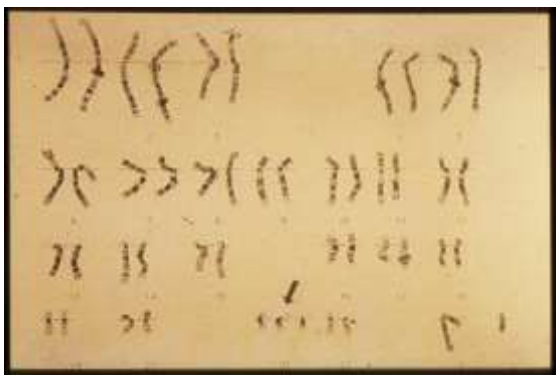
- Smoking
- Drogs and alcohol
- Infections, sepsis
- Premature birth
- Peculiar uteral contractions, pains
- Uteral rupture
- Overcarrying of the pregnacy

Fetal diseases and intrauterine death or death at birth

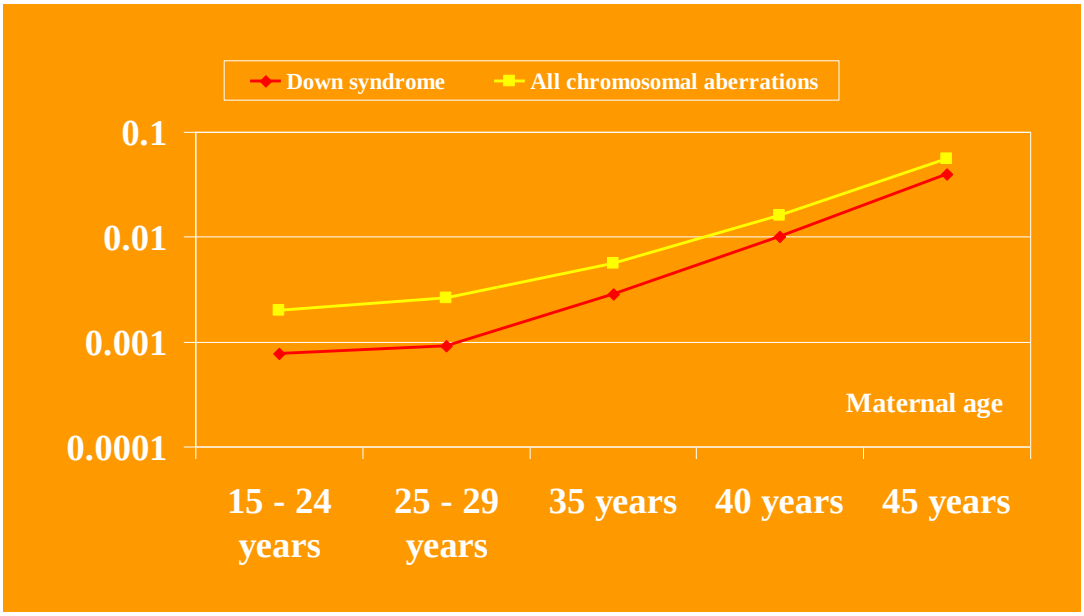
- Major malforations 15-20%
- Feto-maternal bleeding 5%
- Hydrops fetalis
- Fetal arrhytmia
- Alloimmune thrombocytopenia (stroke)
- Rh isoimmunisation

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

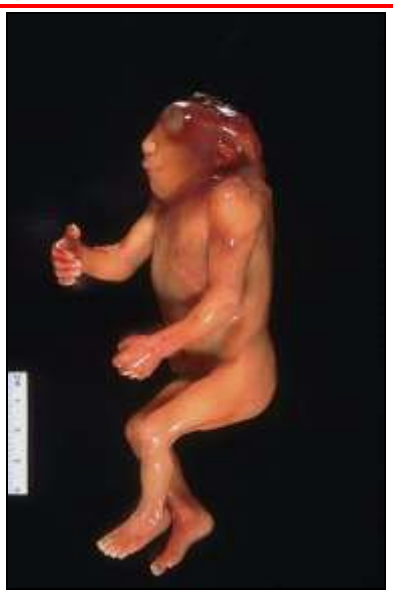


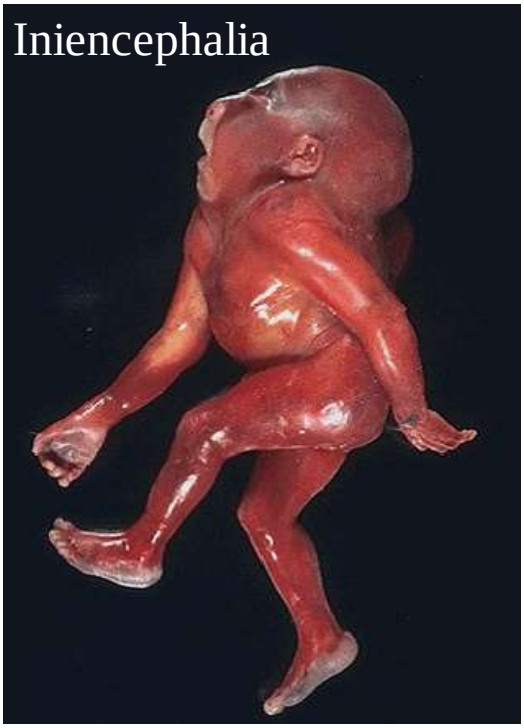
Incidence of chromosomal abnormalities



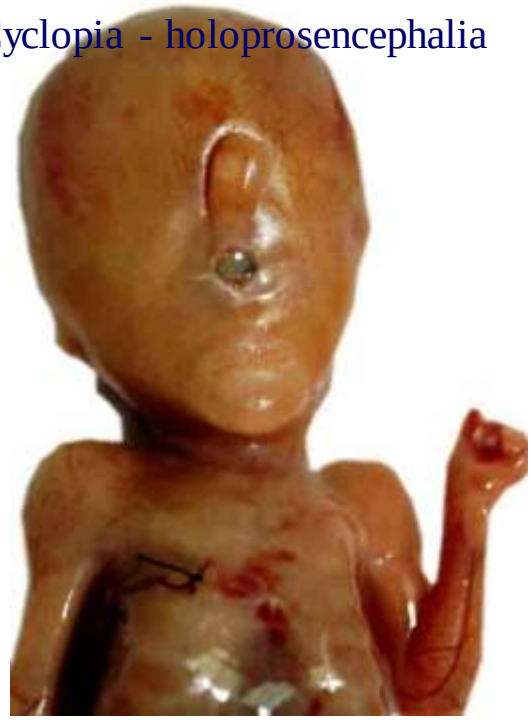
Late miscarriage

- 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
  - Omphalocoele
  - Renal malformations, urethra obstruction
  - Cardiac abnormalities
- The cause is usually unknown – congenital malformations are not sufficient!





Cyclopia - holoprosencephalia

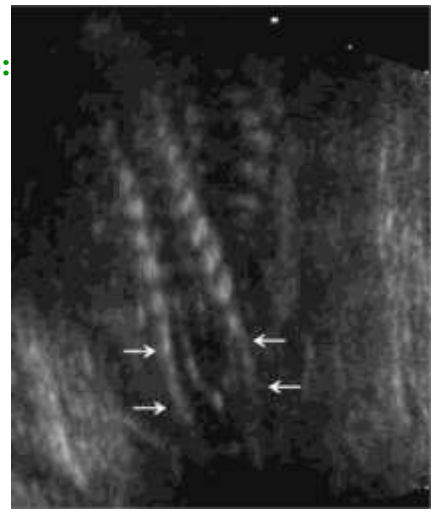


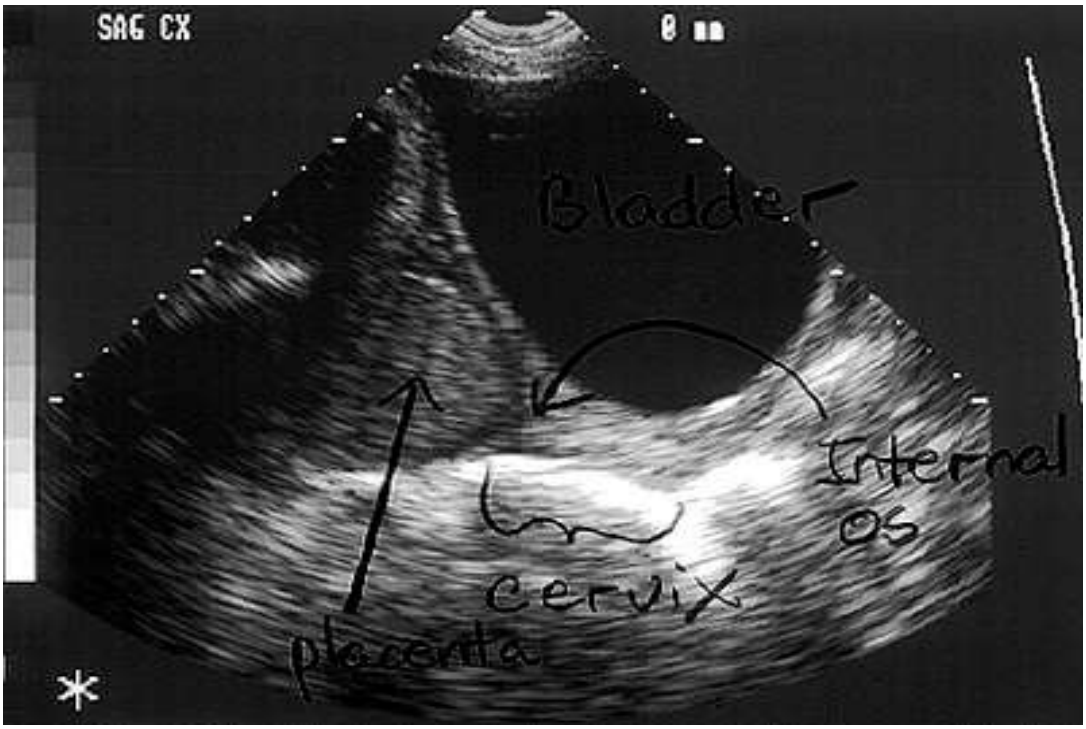
Diagnosis of the developmental disorders

- **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 pregnany with malformations

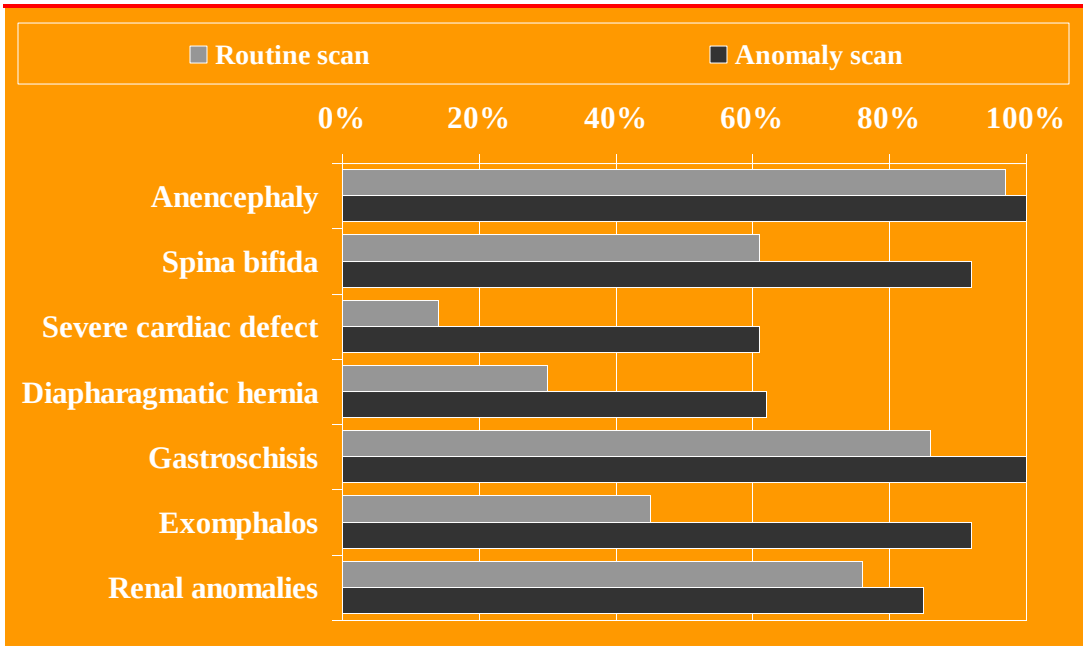
Mid-gestation ultrasound scan

- Becoming a standard procedure, between 18th and 22nd 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



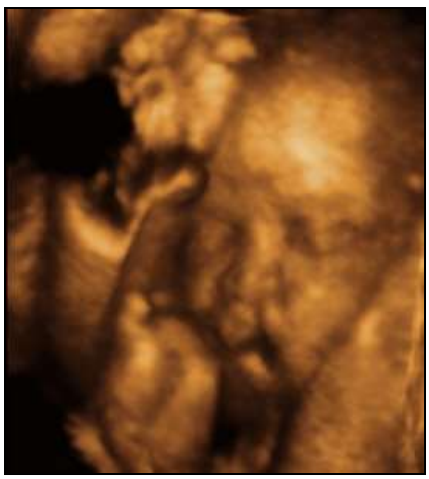
Results of the anomaly scan

- Normal foetal development, no detectable anomaly
- Significant malformation:
  - •Severe cardiac defect
  - •Neural tube defect
  - •Amnion band sequence

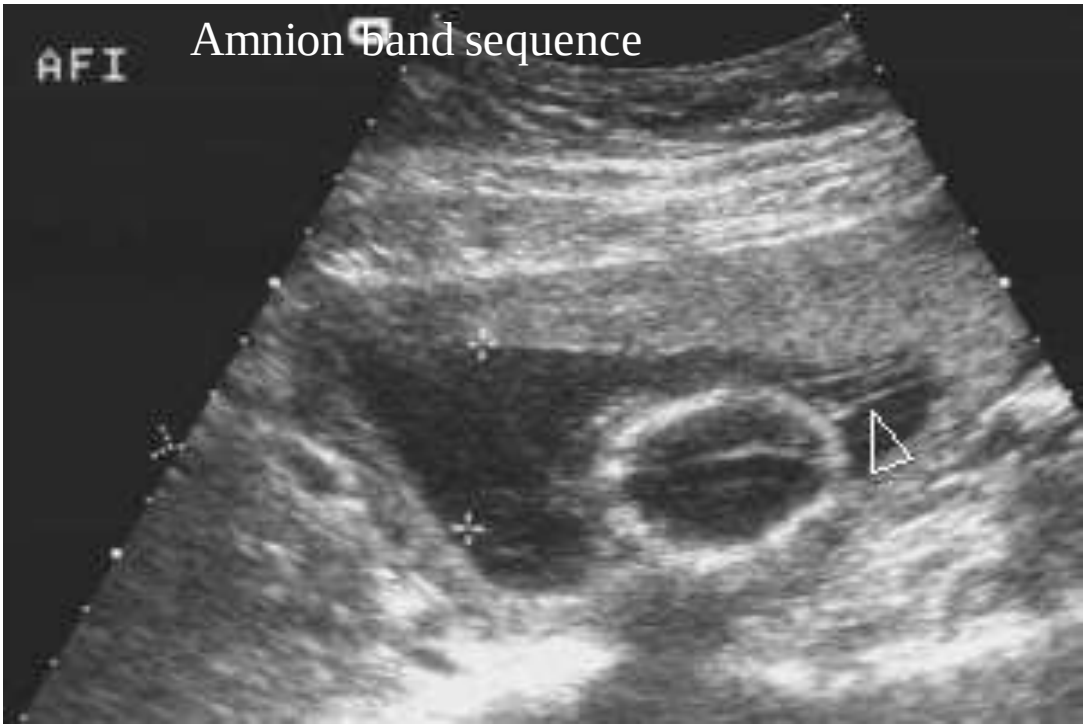
  –Termination of pregnancy
- Non-lethal malformation

  –May be part of a single gene disorder, chromosomal defect or sequence!

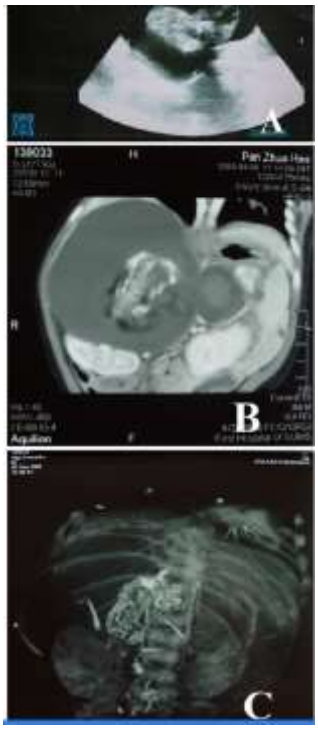
  –Short femur, exomphalos, gastroschisis, facial clefts



•Further testing – amniocentesis (12 weeks), chorion villous biopsy (18-20 weeks), genetic referral



Amnion band sequence



Abdominal Imaging

Fetus-in-fetu: imaging and pathologic findings

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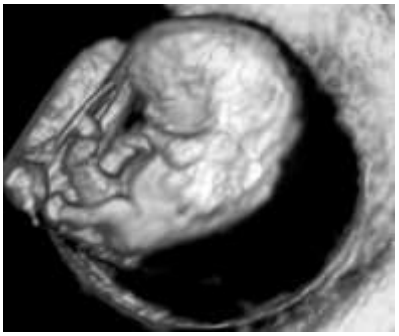
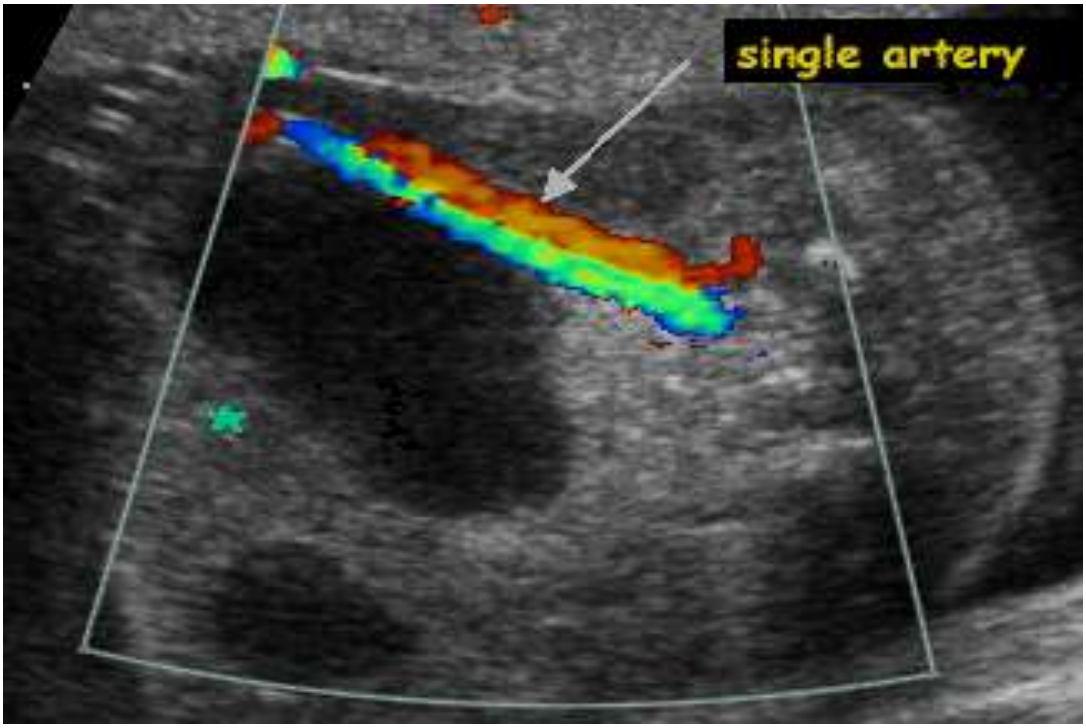
Results of the anomaly scan

- 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

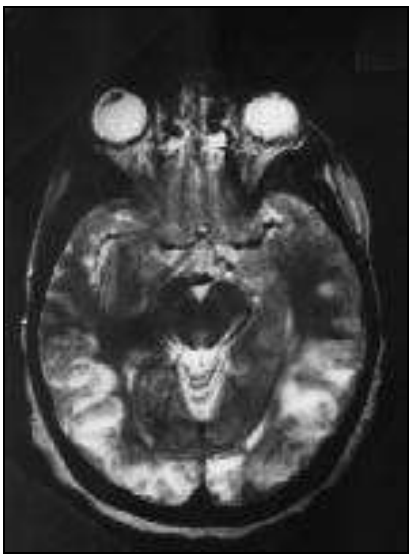
- From 24 weeks to birth
- Protected position
- Factors influencing foetal growth:
  - Nutrition, oxigenation, potential to develop
  - Foeto-materno-placental unit
    - Foetal disorders
    - Maternal factors
      - Diseases
      - Social factors
    - **Placenta**
  - Environmental factors

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

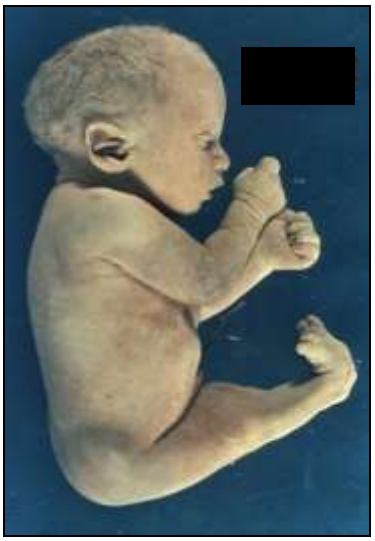
PIH, PET, HELLP

- 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 enyzmes, low platelet (HELLP)
- Aetiology:
  - Failed remodelling of the decidual vessels
- Treatment and prevention
  - Magnesium



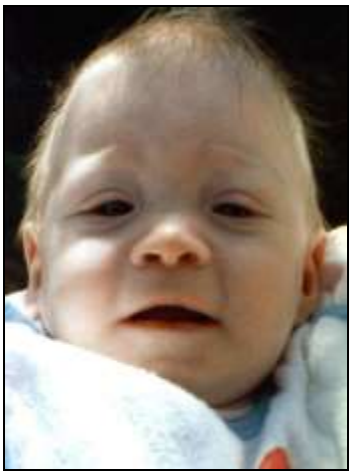
Maternal diabetes

- 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



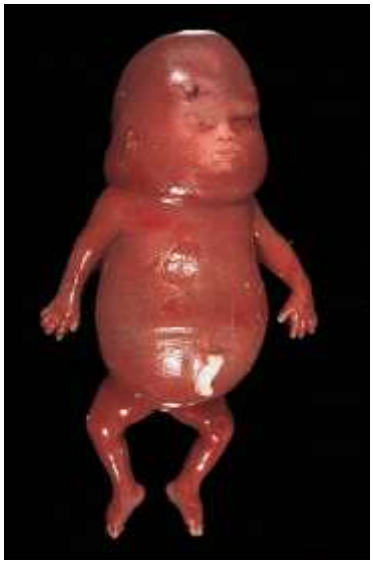
Foetal alcohol syndrome

- 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

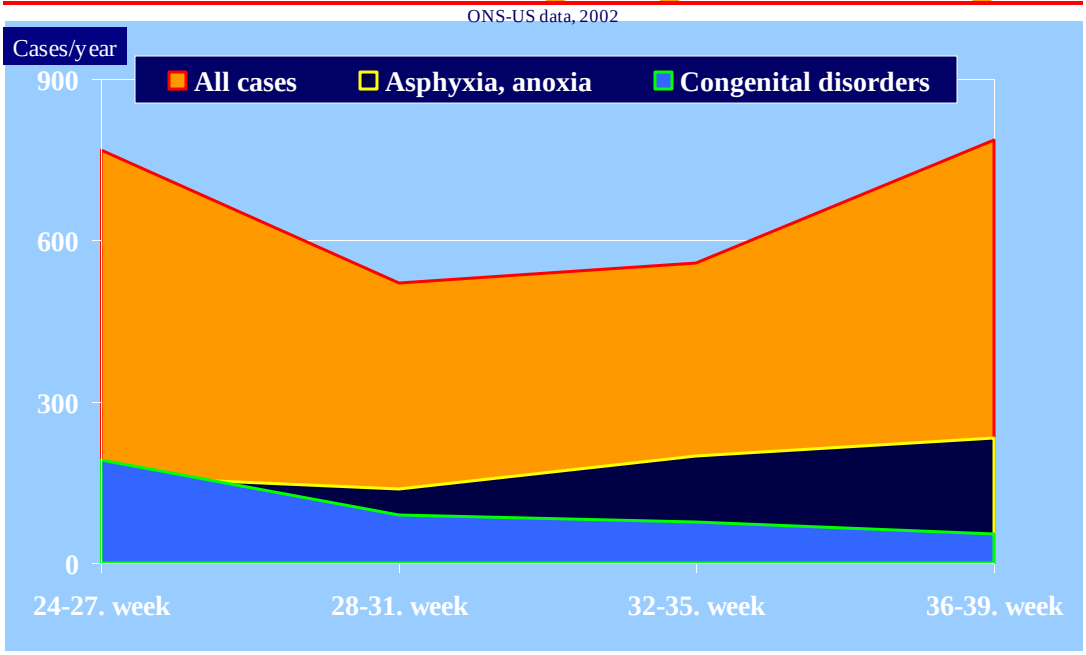
- Generalized oedema of foetus and placenta
- Can be associated with a cystic hygroma
- Causes:
  - Transplacental infection
    - Parvovirus B19, CMV
  - Inherited haemoglobinopathies
    - Thalassaemia
  - Blood group dyscrasias
    - Rh factor incompatibility
  - Chromosomal anomalies
    - Turner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



Consequences of intrauterine stress

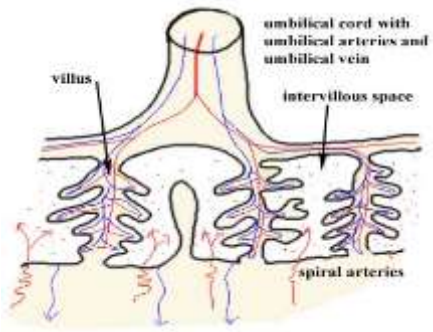
- Chronic stress:
  - Low birthweight
    - SGA/IUGR
  - Prematurity
  - Stillbirth
- Acute stress:
  - Meconium release
  - Hypoxic haemorrhages
  - Foetal death, stillbirth
  - Prematurity

Stillbirths according to gestational age



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

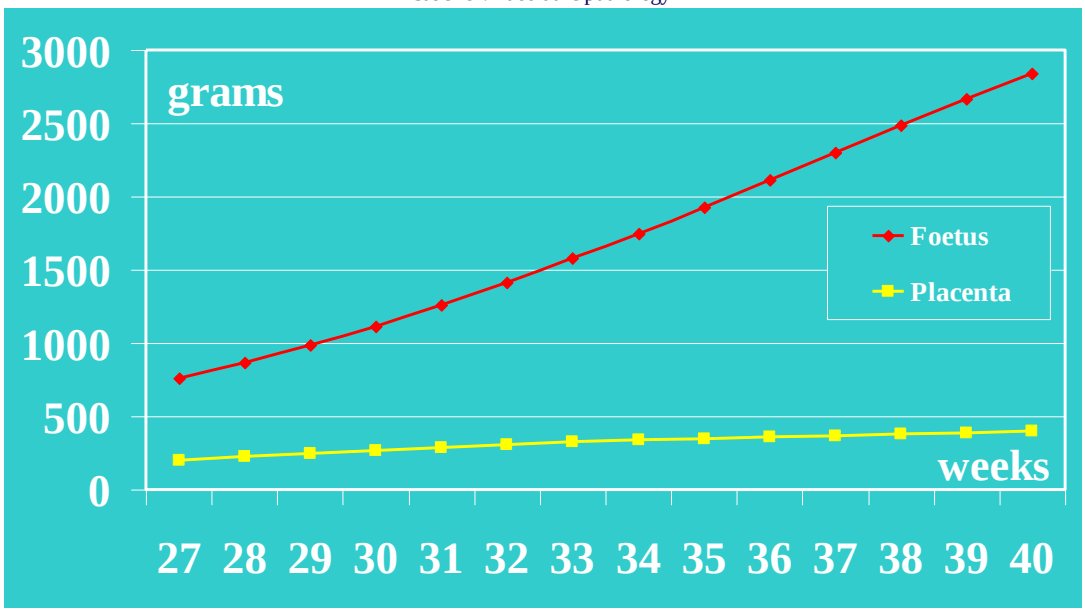


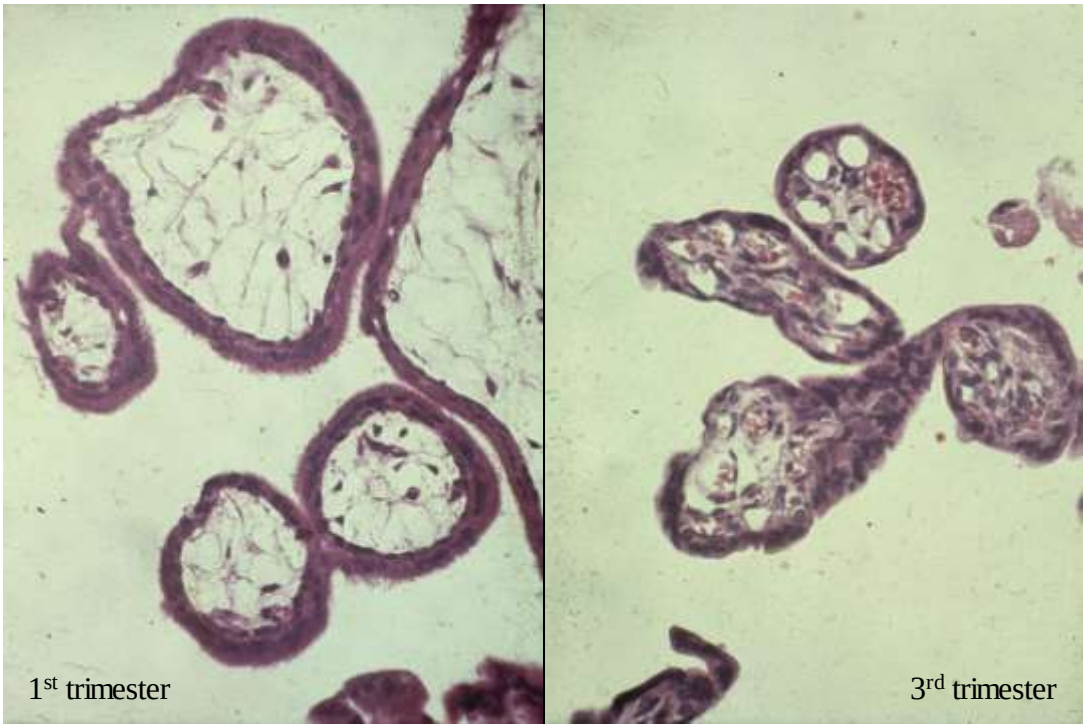
- (Functions of the foetal organs:
  - Lungs and intestines: maturation
  - Kidneys: production of amniotic fluid

  (oligohydramnion, polyhydramnion (CAVE: CMV!)
  - Liver: haematopoesis)

Weight development of foetus and placenta

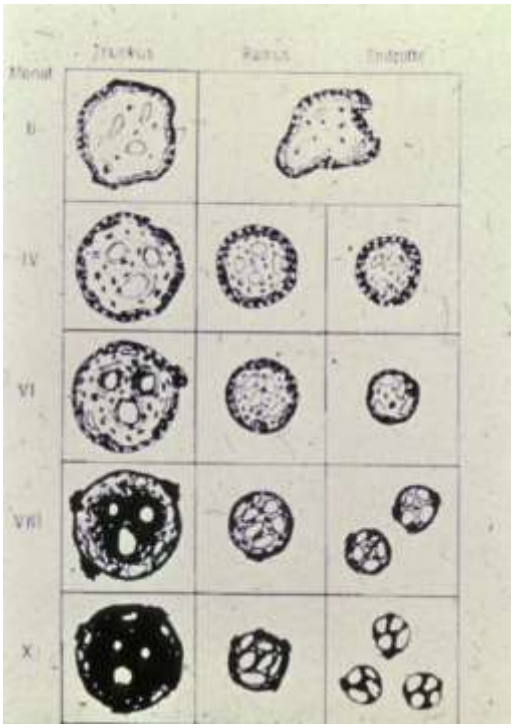
Stocker: Paediatric pathology





I. Placenta

- Stucture
  - Maturation disorders
  - Implantation disorders
  - circulation
  - inflammation
  - Proliferative changes (gestation trophoblast diseases)
- Placenta insufficiency



Development of placenta:

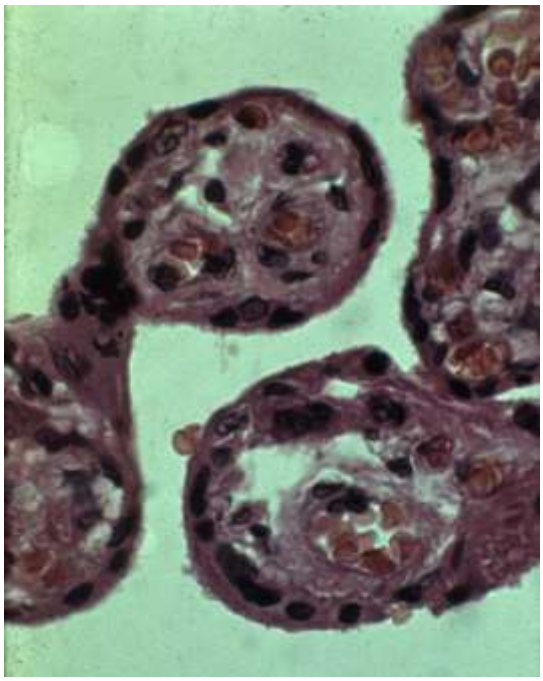
Primary villus

Secundary villus

- Stroma rich
- Vessel are central
- Double trophoblast layer

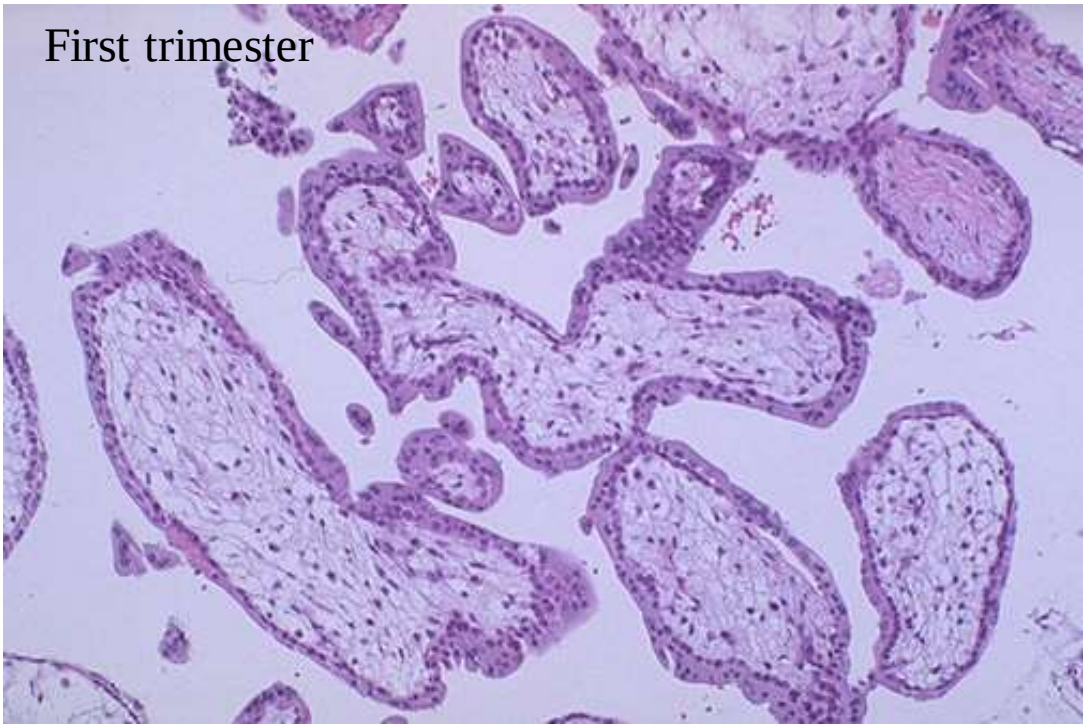
Tertiary villus

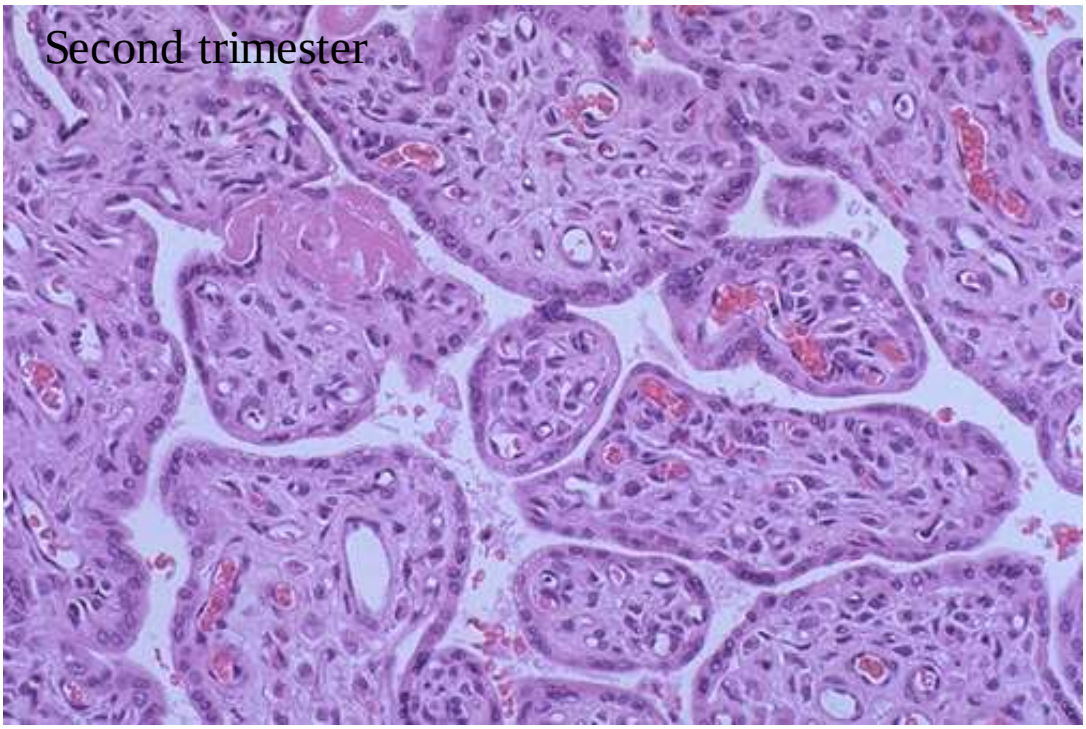
- Scanty of stroma
- Sinusoids
- Syntitio1capillaris membrane
- Big surface ratio

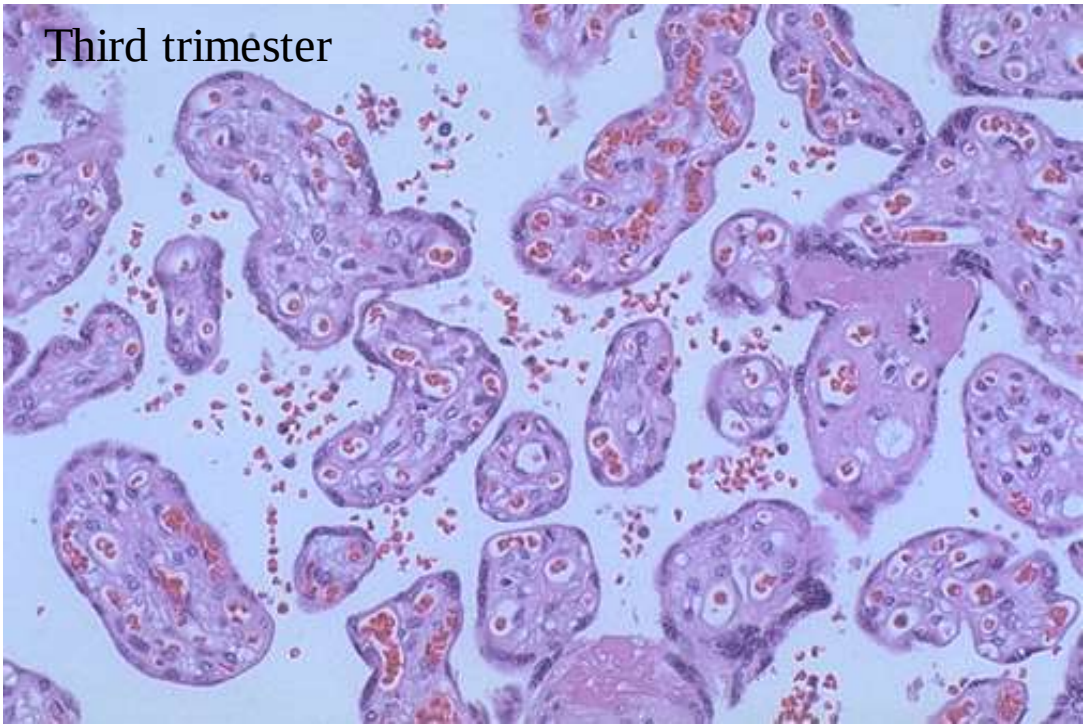


Placenta pathology I.

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

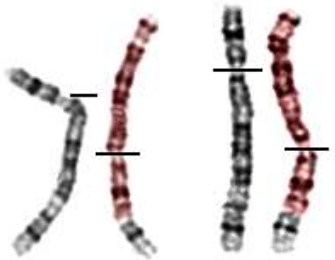

First trimester


Second trimester

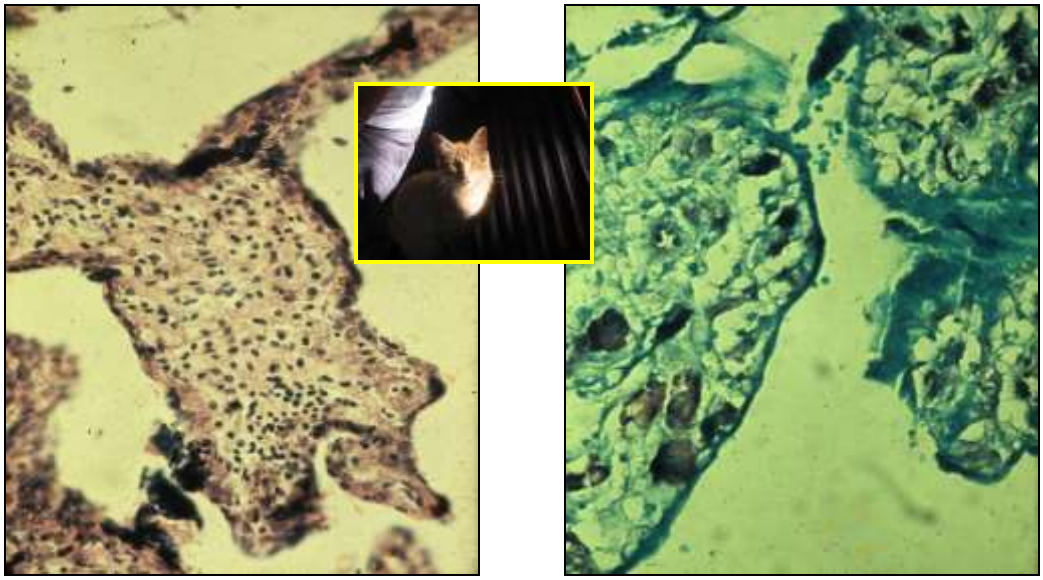


Maturity disorders

- 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

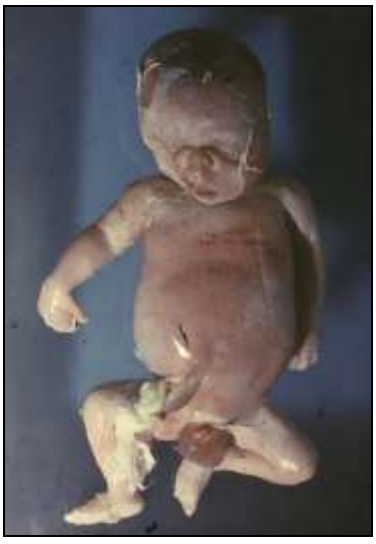


Toxoplasma placentitis



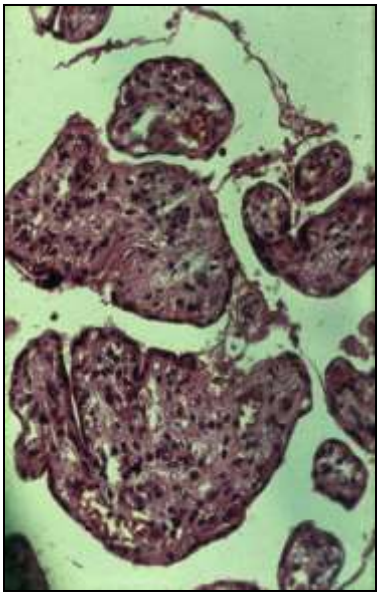
Acute placenta insufficiency.

- Cause:
  - Maternal circulatory shock
  - Large placenta infarction
  - Retroplacental haematoma
- Result:
  - Acute fetal hypoxia
  - Petechial haemorrhages
  - Brain oedema
  - Intrauterine death



Subacute placenta insufficiency.

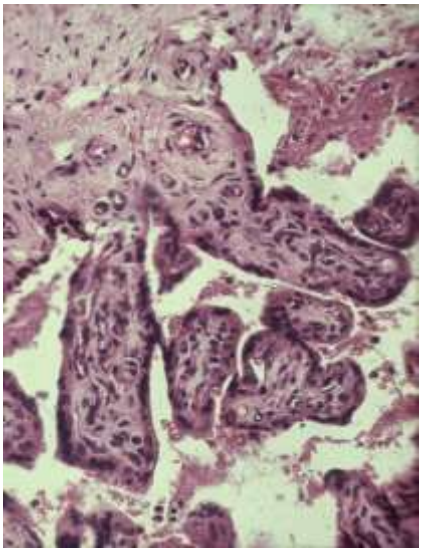
- Cause:
  - Maternal cardial or respiratory insufficiency
  - Multiplex small placenta infarction
  - Inflammations
  - Placenta developmental disorders
- Result:
  - Intrauterine death
  - Premature birth
  - Intrauterine retardation



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.

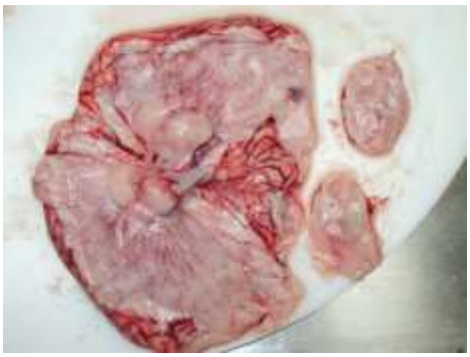
Pathology of the umbilical cord

- Mechanical trauma:
  - knots, pseudoknots, torsion, rupture
- Rupture caused by placenta praevia
- Vascular anomalies:
  - Vessel thrombosis
  - Aneurysm, rupture
  - One umbilical artery: sign of fetal malformations

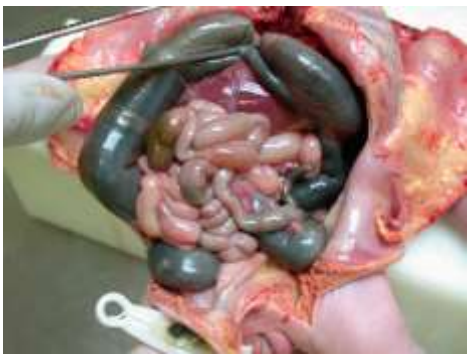
Dysruptions

- **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

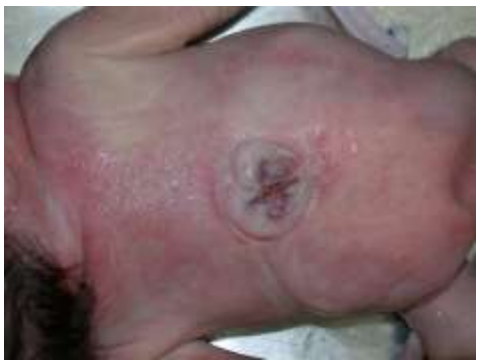


Hydrocephalus internus



atresiák

Meningocele, spina bifida



multiple developmental disorders

- **two or several ogansystems are involved, the ethiology of the damage is the same**
- **Reason:**
  - **Infection** (**TORCH complex, varicella**)
  - **Chemicals**
  - **Aberration of chromosoms**
  - **e.g.: rubella (German measles) syndrom, fetal alcohol (consumption) syndrom, thalidomide (Contergan)**

ZIKA VIRUS

CDC has updated its interim guidelines for healthcare providers in the United States caring for infants and children with possible congenital or perinatal Zika virus infection. These guidelines include recommendations for the evaluation, testing, and management of infants and children with possible Zika virus infection. These interim guidelines will be updated as more information becomes available.
Update: Interim Guidelines for Healthcare Providers Caring for Infants and Children with Possible Zika Virus Infection - United States, February 2016

What is different in these updated guidelines?

Updated guidelines contain a new recommendation to provide routine care to infants with no abnormal findings on prenatal or postnatal ultrasound, normal physical examination and whose mothers were not previously tested for Zika virus infection. Updated guidelines also contain new recommendations for the care of infants and children with possible acute Zika virus disease.

Why is CDC updating clinical guidelines?

CDC continues to evaluate all available evidence and to update recommendations as new information becomes available. CDC's updated guidelines have been informed by our close collaboration with clinicians, professional organizations, state and local health departments, and many other stakeholders.

When is an infant or child at risk for Zika virus infection?

An infant or child who has traveled to or resided in an area with ongoing transmission of Zika virus is at risk for Zika virus infection. Additionally, an infant whose mother was infected with Zika virus during pregnancy is at risk for Zika virus infection *in utero*. Infants can also be infected perinatally if the mother traveled to or resided in an area with Zika virus transmission within 2 weeks of delivery.

Zika Virus Evaluation and Potential Outcomes

What should healthcare providers do to evaluate infants with positive or inconclusive Zika virus test results?

A thorough physical examination should be performed, including careful measurement of the head circumference, length, weight, and assessment of gestational age. Cranial ultrasound is recommended unless it was performed as part of prenatal screening in the third trimester and clearly showed no abnormalities of the brain. Ophthalmologic evaluation is recommended as well as newborn hearing screen. An evaluation for neurologic abnormalities, dysmorphic features, splenomegaly, hepatomegaly, and rash or other skin lesions is also recommended. Full body photographs and any rash, skin lesions, or dysmorphic features should be documented. If an abnormality is noted, consultation with an appropriate specialist is recommended.

What additional follow-up is recommended for children with microcephaly, intracranial calcifications or abnormal neurologic findings?

Consultations are recommended with a clinical geneticist or dysmorphologist, a pediatric neurologist, and a pediatric infectious disease specialist. A complete blood count including platelet count, and tests for liver enzymes and function should also be conducted. Testing for other congenital infections is also recommended. If any additional congenital anomalies are identified through clinical examination and imaging studies, genetic and other teratogenic causes should be considered.

If a mother had Zika virus infection during pregnancy but her newborn tests negative for Zika virus, what is recommended for additional follow-up?

In the absence of abnormal findings on examination, the infant should receive routine pediatric care including measurement of growth and development, and appropriate evaluation and follow-up for any clinical findings that arise. If the newborn has abnormal findings on examination, diagnostic testing for other causes of the newborn's conditions should be performed including testing for other congenital viral infections if indicated.

Is there any information on neurocognitive outcomes in neonates if they are exposed to Zika virus during labor and delivery or after birth?

Perinatal transmission of Zika virus infection has been reported. However information is limited to two cases: one of these infants was asymptomatic and the other had thrombocytopenia and a diffuse rash. Evidence from other flaviviruses, such as West Nile virus and dengue virus, indicate that transmission has resulted in findings in the neonate ranging from no symptoms to severe illness (including fever, thrombocytopenia, and hemorrhage). The spectrum of clinical features that might be observed in infants who acquire Zika virus during the perinatal period is currently unknown.

What is the prognosis for a newborn with congenital Zika virus infection?

The prognosis for infants with congenital Zika virus infection is not known.

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 infecti
  - Outcome:
    - Foetal death
    - Prematurity
    - Congenital infection – foetal pr
- Chronic villitis/intervillositis
  - TORCH complex, VUO
  - (villitis of unknown origin)
  - Outcome:
    - Early infection – teratogenesis
    - Late infection:
      - Foetal death
      - Hydrops (eg. Parvovirus B19)
      - **Assymetric intrauterine g**

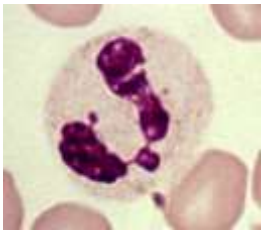
Premature rupture of membranes (PROM) is a spontaneous break or tear in the amniochorial sac before onset of regular contractions, resulting in progressive cervical dilation. Labor usually starts within 24 hours; more than 80% of these neonates are mature. The latent period (between membrane rupture 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

- Acut chorioamnionitis
  - Ascending infection – genital tract /direct contamination , rupture
    - Early amniotic rupture
    - death
    - Premature birth
    - Congenitál infection – pneumonia - IRDS

- Chronic villitis/intervillositis
  - TORCH complex/VUO (villitis of unknown origin)
    - Early infection – teratogious
    - Later infection:
      - death
    - Hydrops (pl. Parvovirus B19)
    - **Assymetric devlopmental disorder (IUGR)**

Acute chorioamnionitis

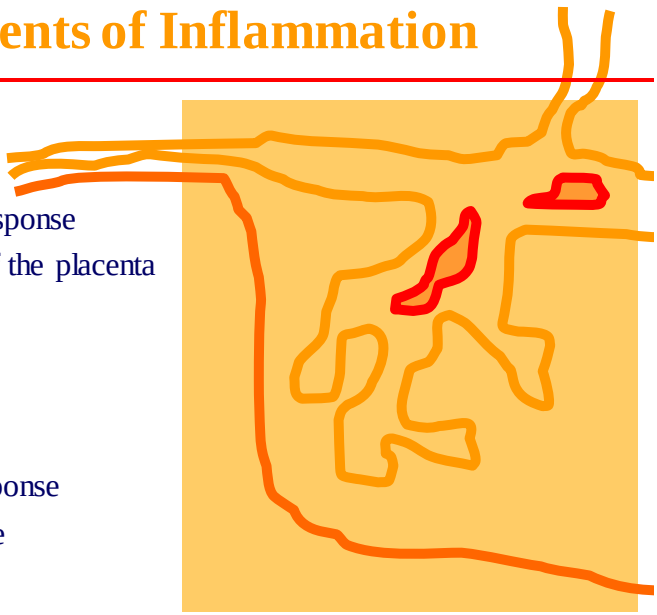


- Simple diagnosis ?

– 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

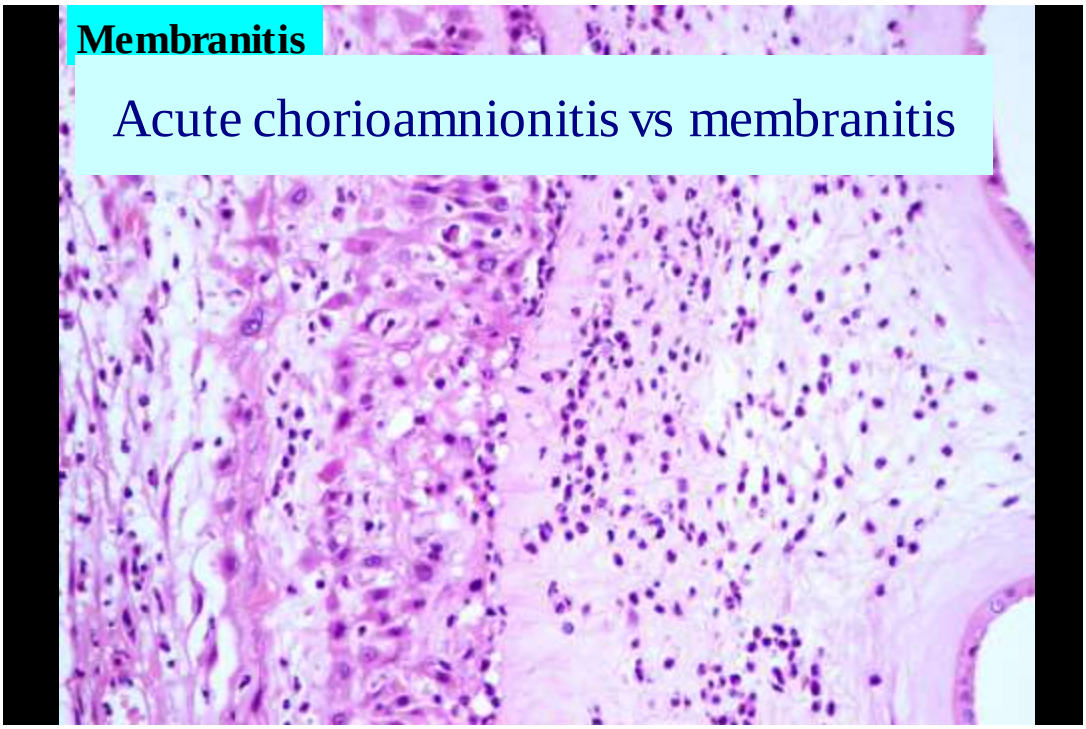


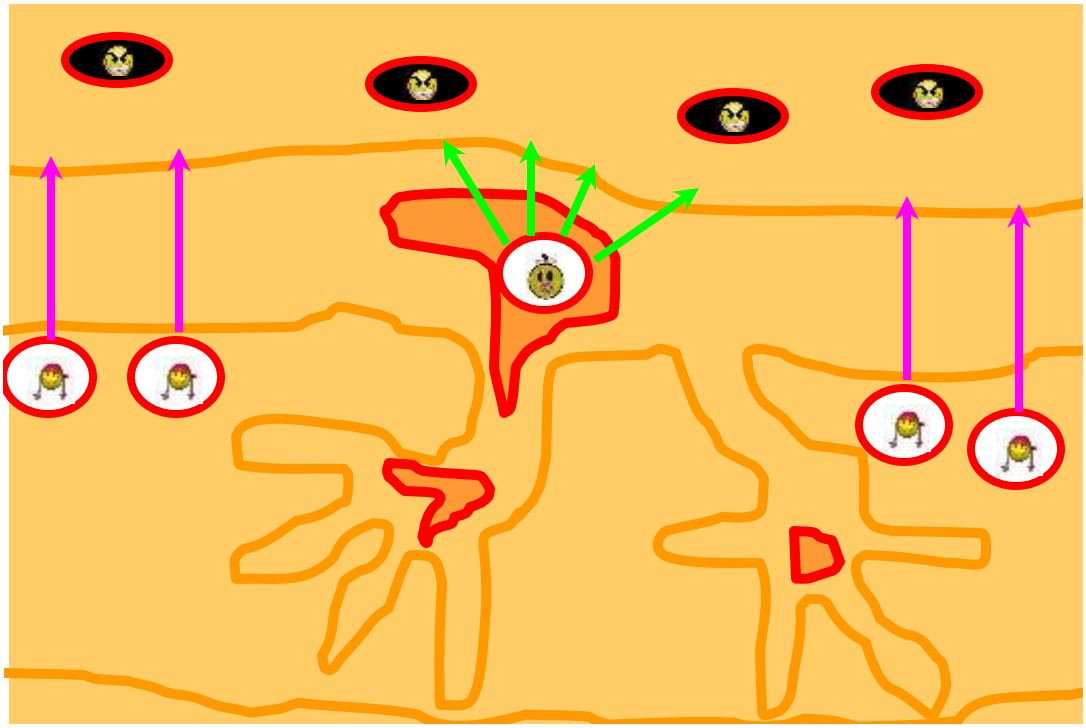
- Fetal membranes
  - – Maternal inflammatory response
  - – Reaction of detachment of the placenta
- Umbilical cord
  - – Fetal inflammatory response
- Chorion sheet

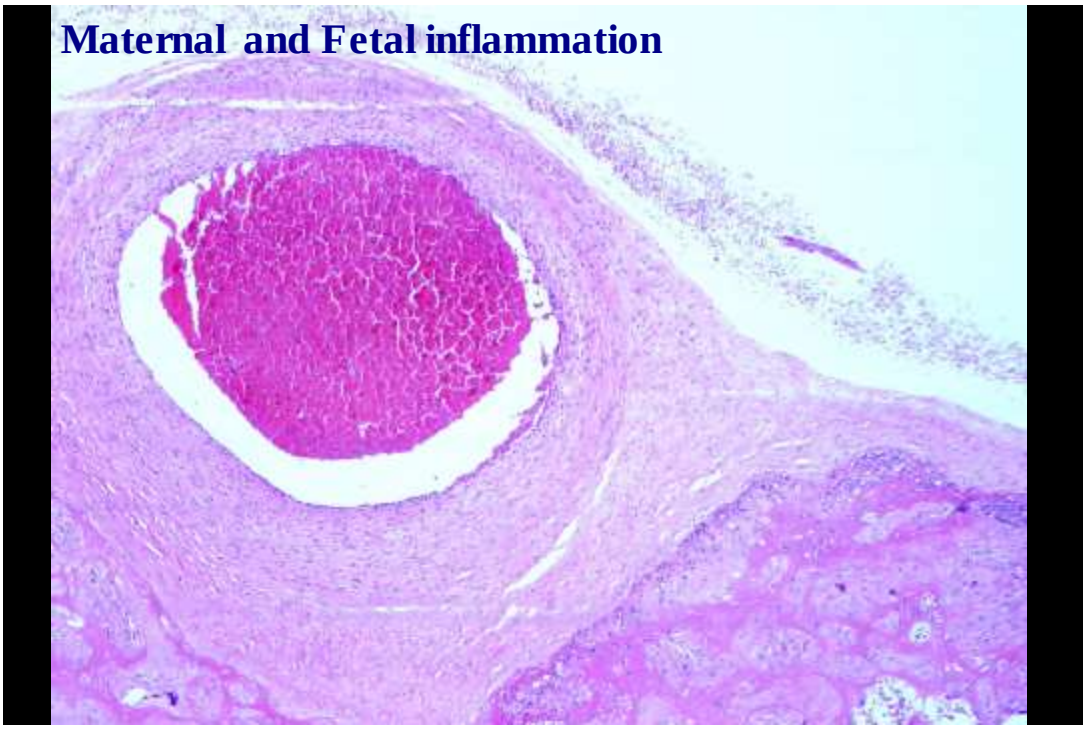
- Maternal inflammatory response
- Fetal inflammatory response

Membranitis

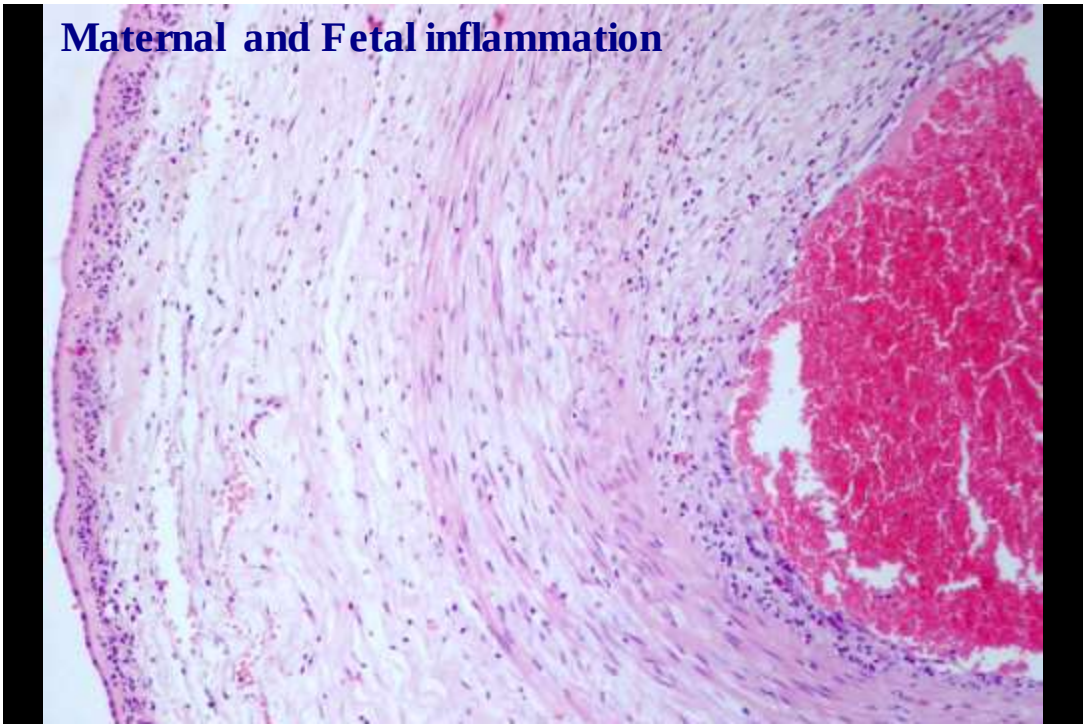
Acute chorioamnionitis vs membranitis



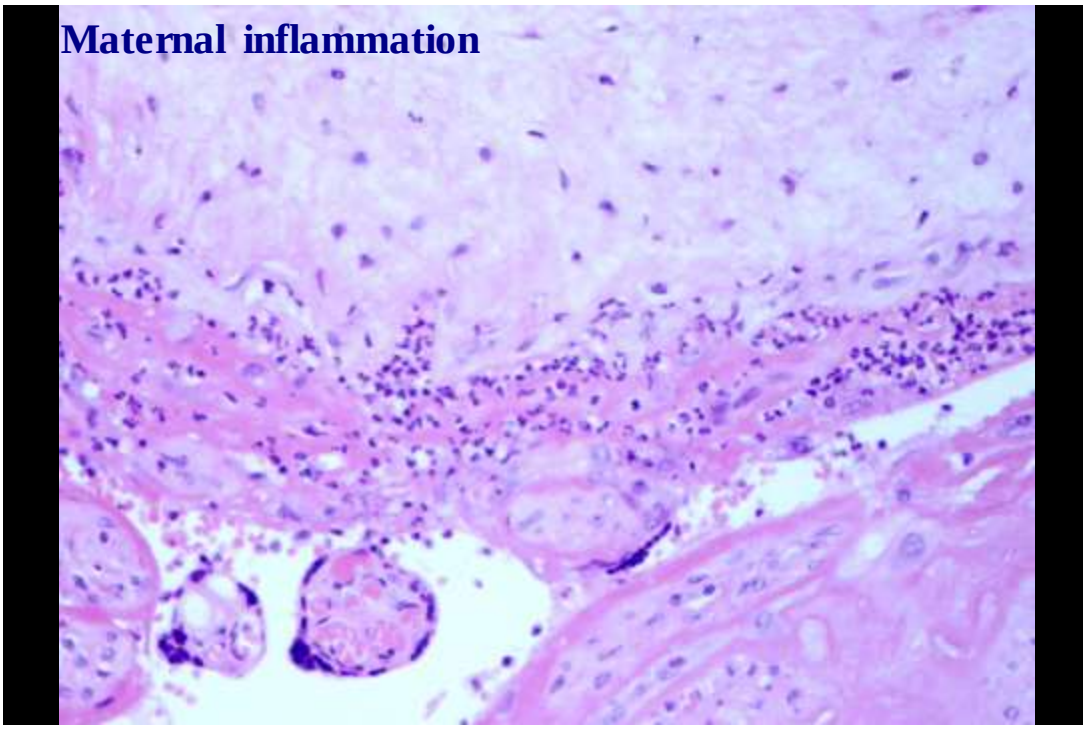


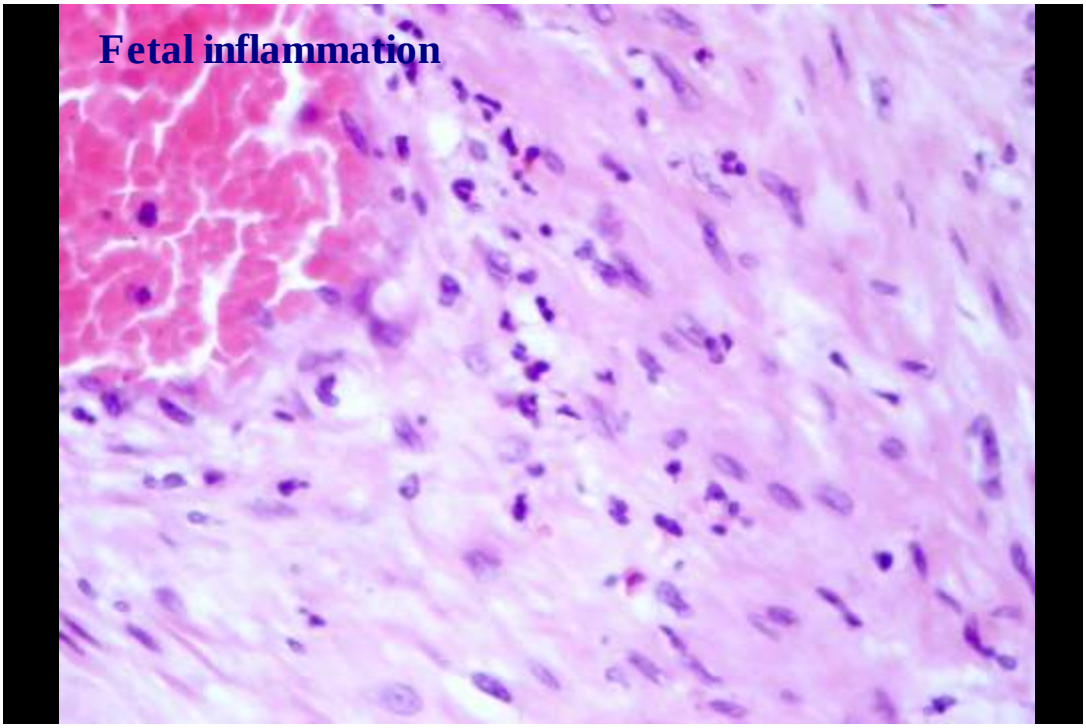

Maternal and Fetal inflammation

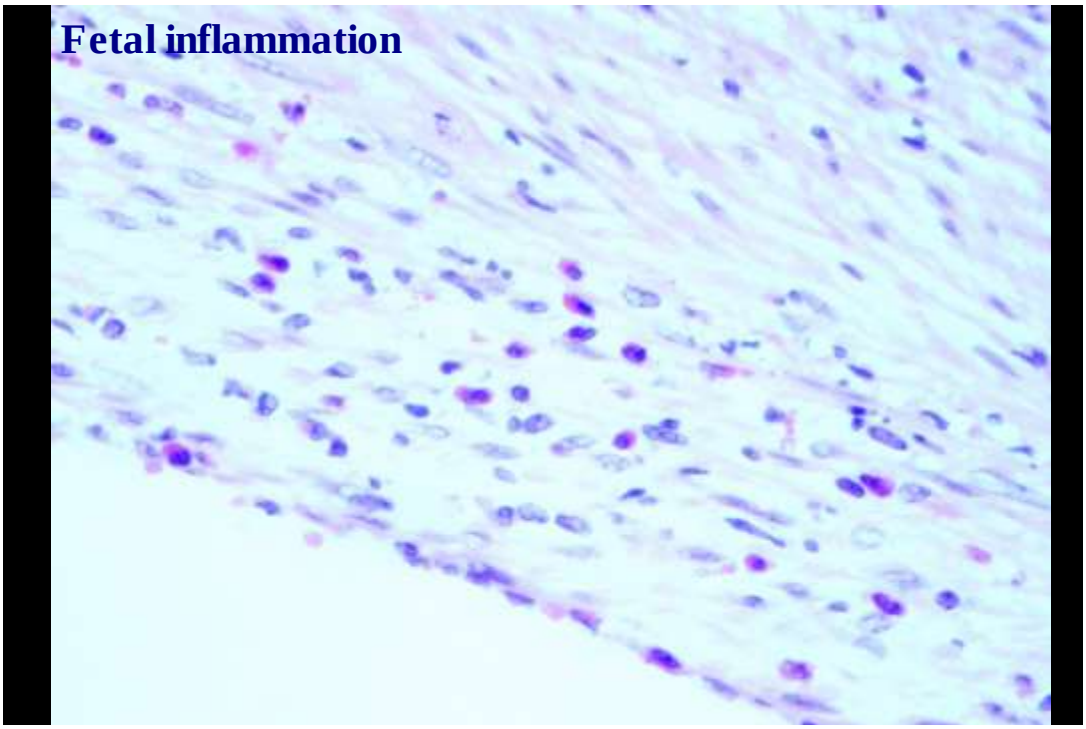
Maternal and Fetal inflammation

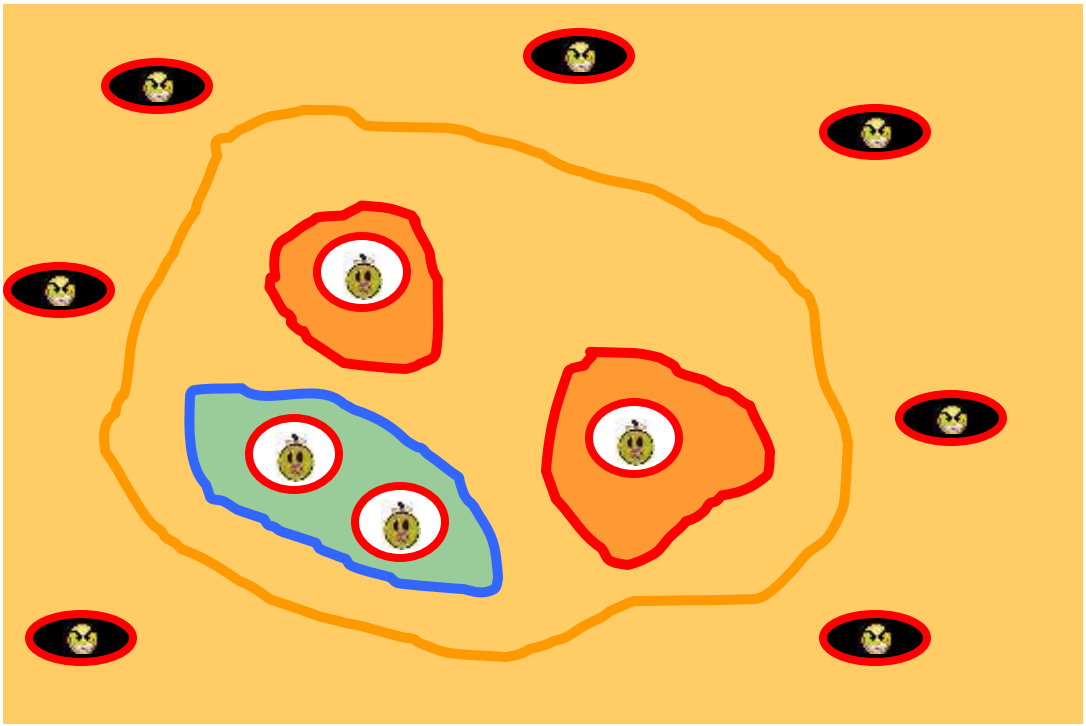


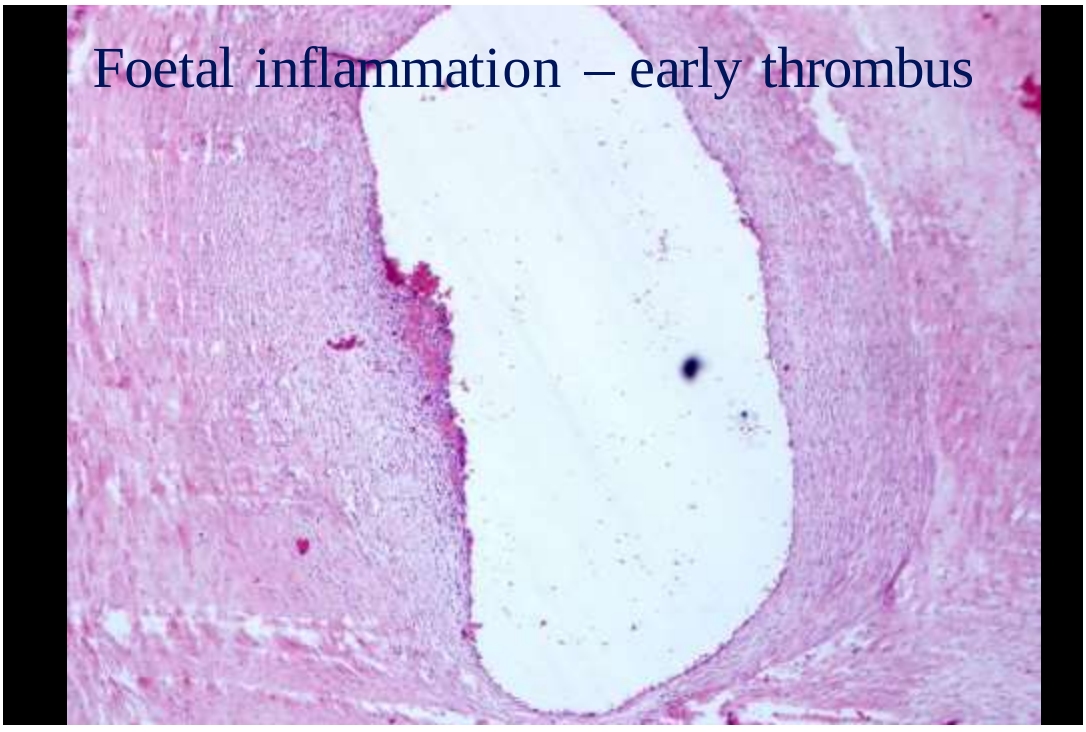
Maternal inflammation

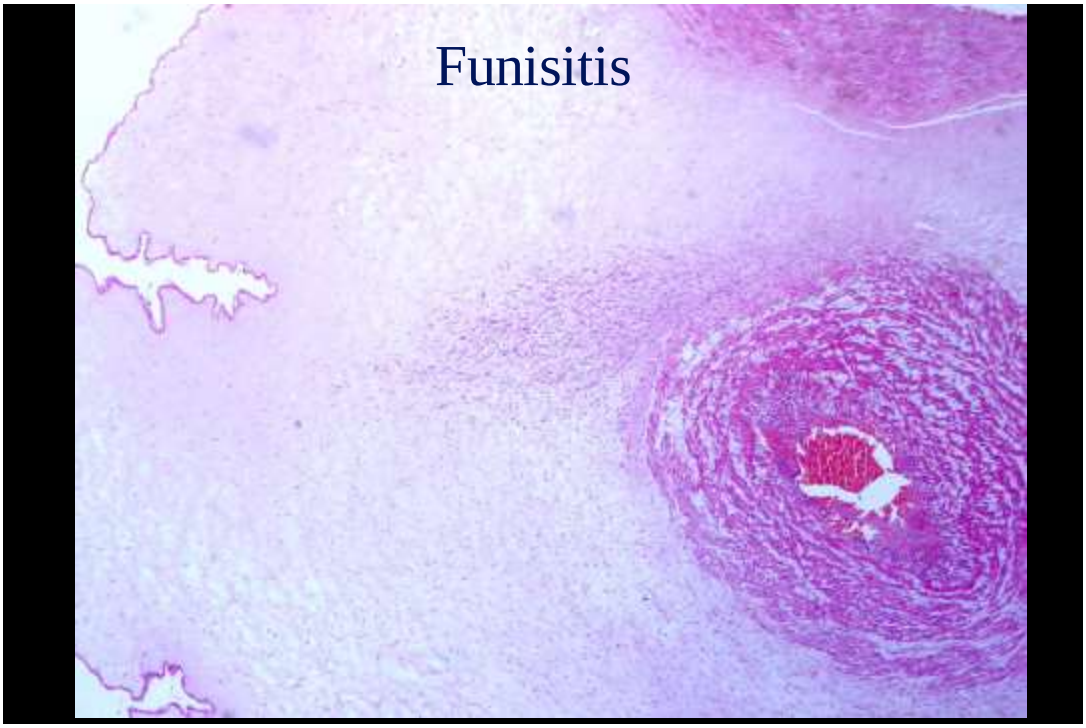


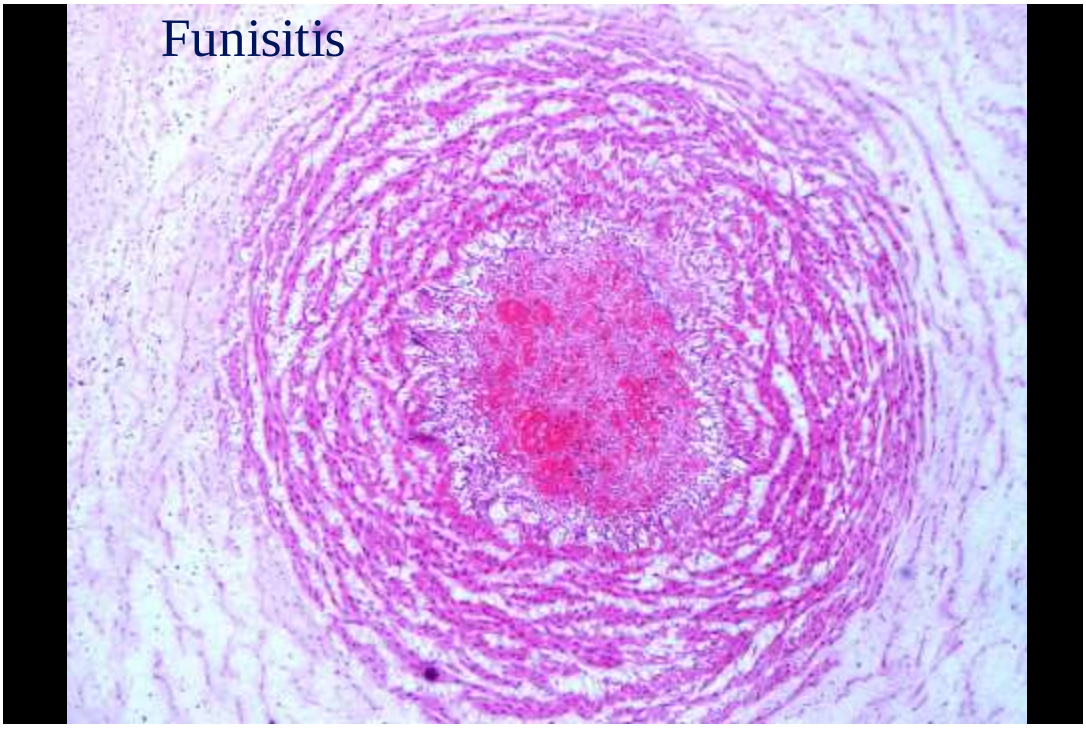

Fetal inflammation

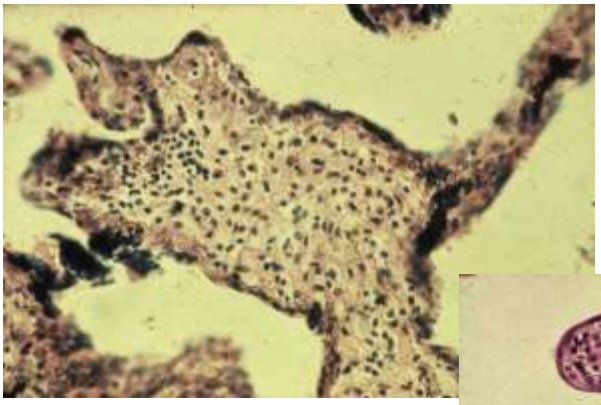

Fetal inflammation

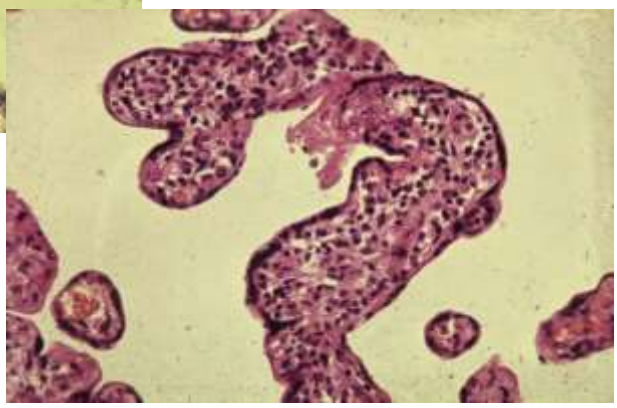


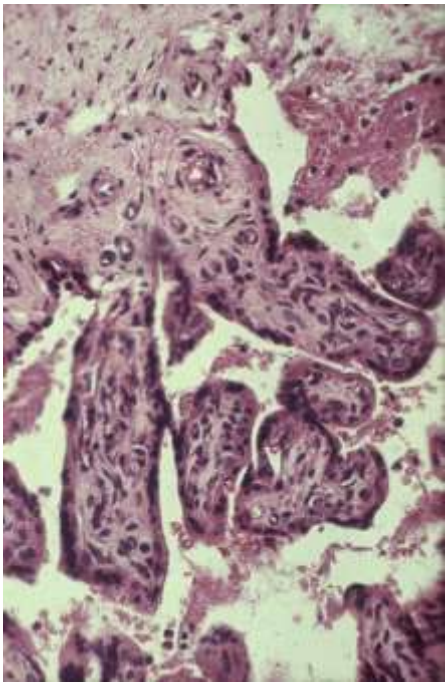

Foetal inflammation – early thrombus

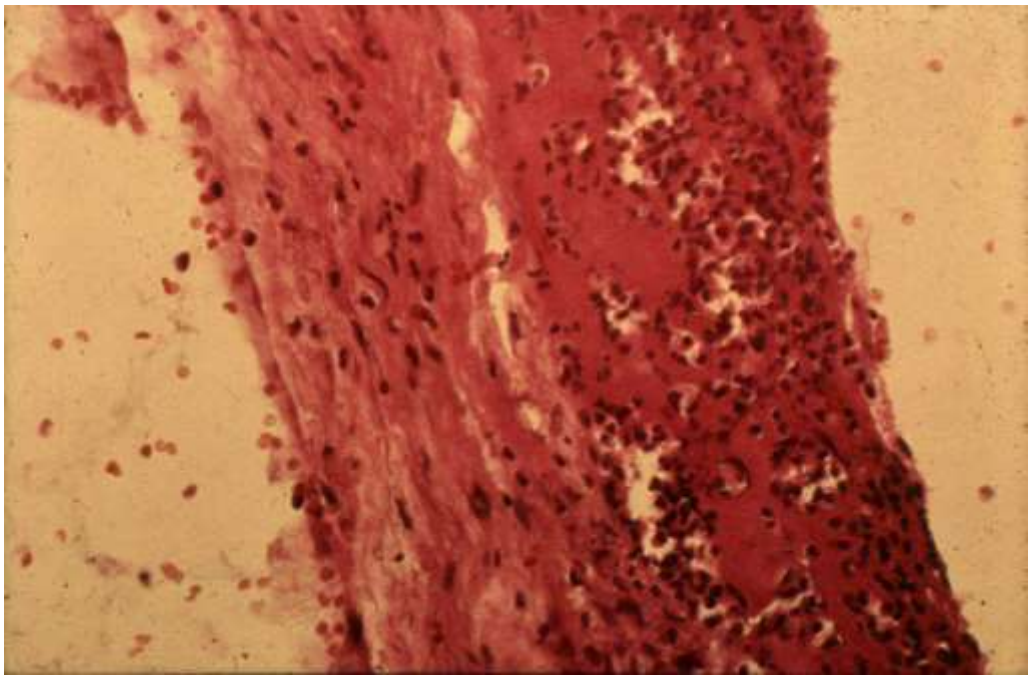

Funisitis

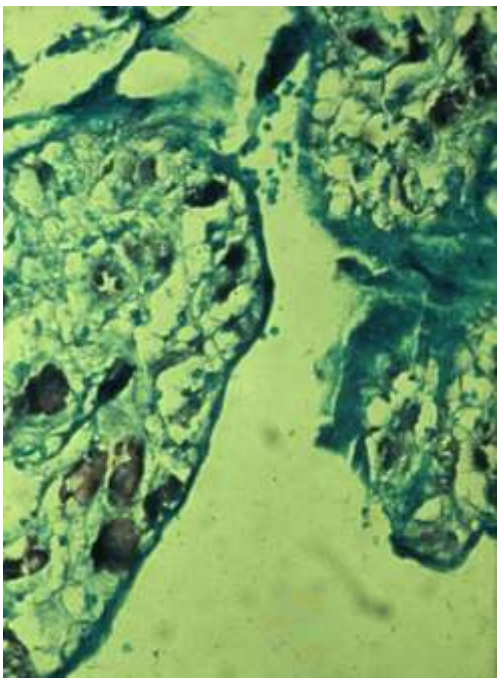

Funisitis

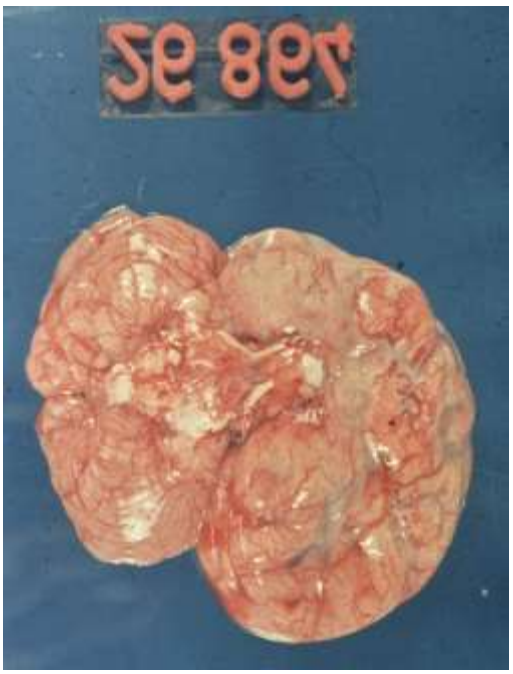






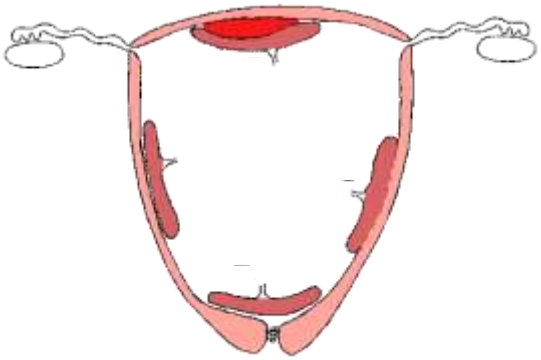






Disorders of implantation

- Depth of implantacion:
  - 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

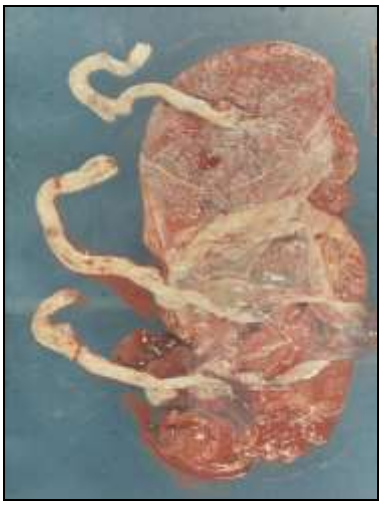
- Foetal vessels:
  - Villous artery thrombosis – inherited coagulopathies
  - Villous damage – loss of foetal blood into maternal circulation
- Maternal vessels – uterine and decidual vessels
  - Infarcts (location, extent)
  - Clots, haemorrhages
  - Intervillous thrombi
  - Placental abruption
  - Subchorionic haematoma

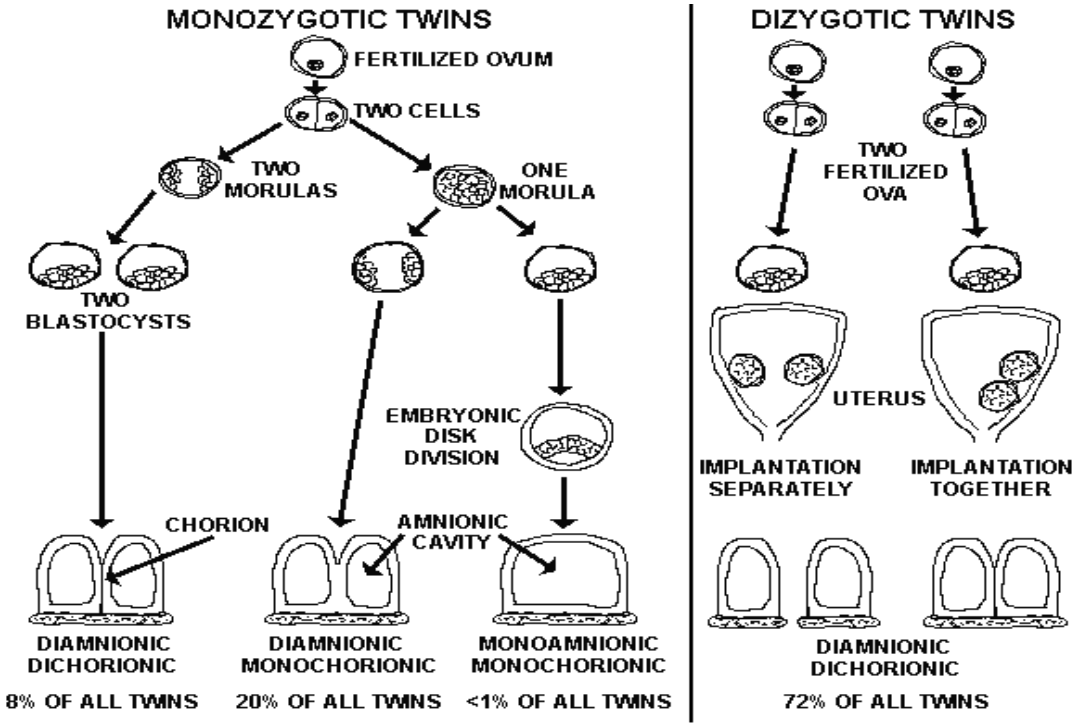
Umbilical cord abnormalities

- 60 cm average (45-75cm)
  - Too long cord:
    - Cord prolapse
    - Cord around neck (suffocation)
    - True knots
  - Too short cord: tension ↑, → 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





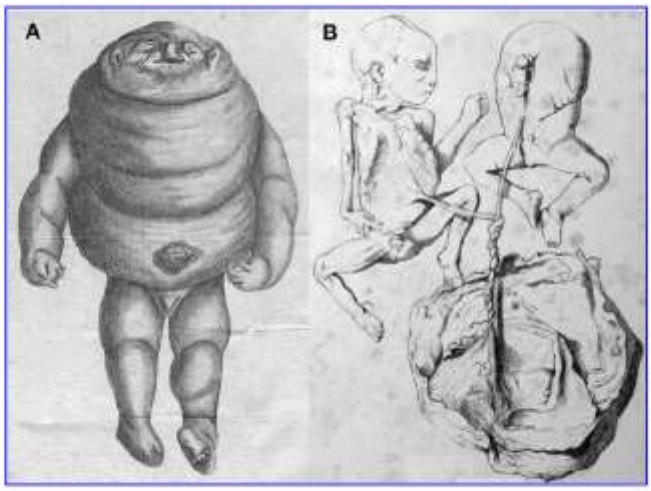
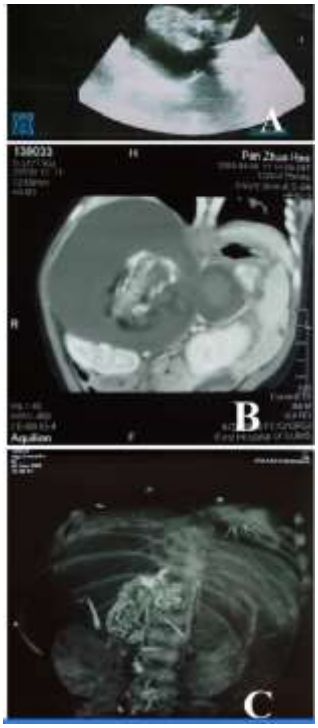


Figure 2 (A) Hydropic acardius anceps "larger and heavier than the accompanying twins", described by Kähler 1777 [18]. (B) acardius acranius with twisted cord depicted by Ahlfeld 1882 to "illustrate the connection of the acardiacus with his twin brother and the placenta" [1].



Abdominal Imaging

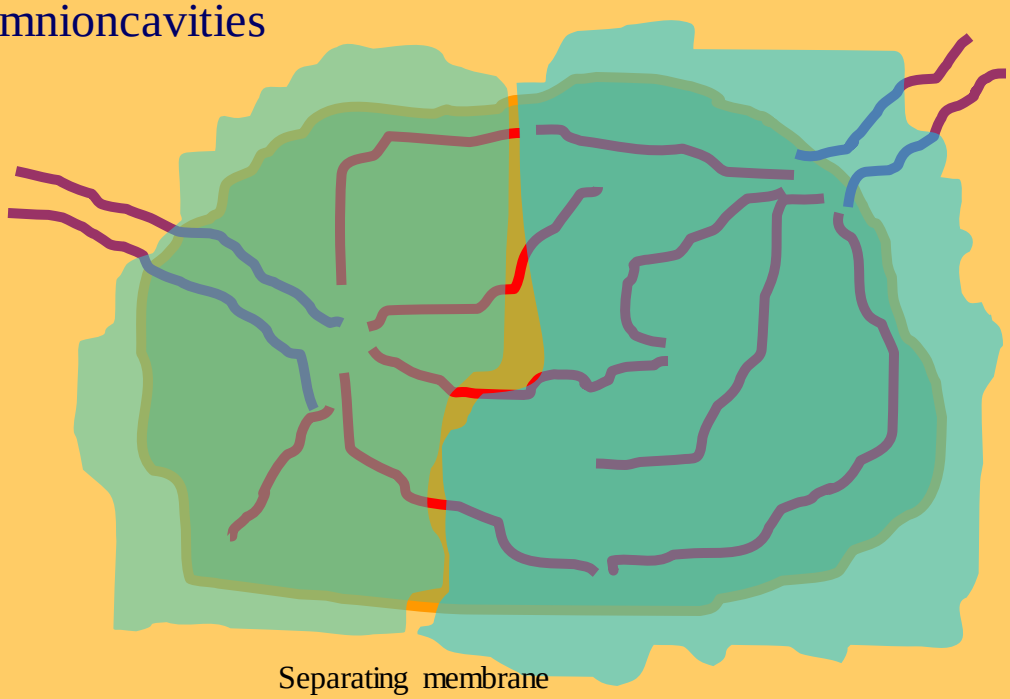
Fetus-in-fetu: imaging and pathologic findings

Junjie Sun, Soulithon VongPhet, Zhichong Zhang, Jiacong Mo

Dangers of twinning

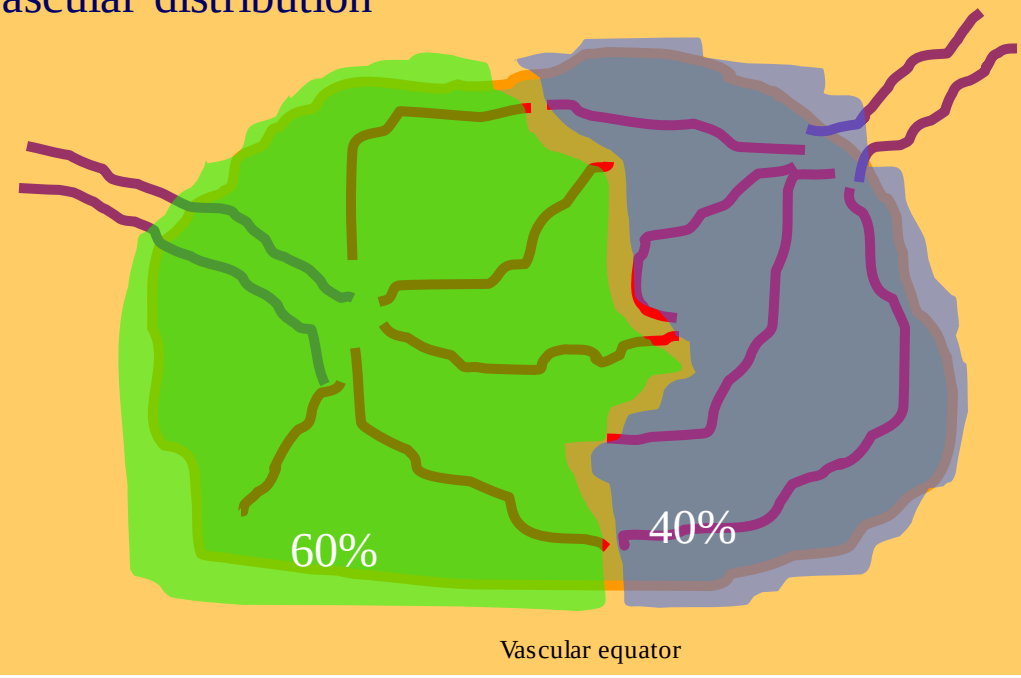
- Conjoined twins
  - Symmetric
    - Craniopagus
    - Thoracopagus
    - Pygopagus
  - Asymmetric
    - Acardius amorphus

Amnioncavities



Separating membrane

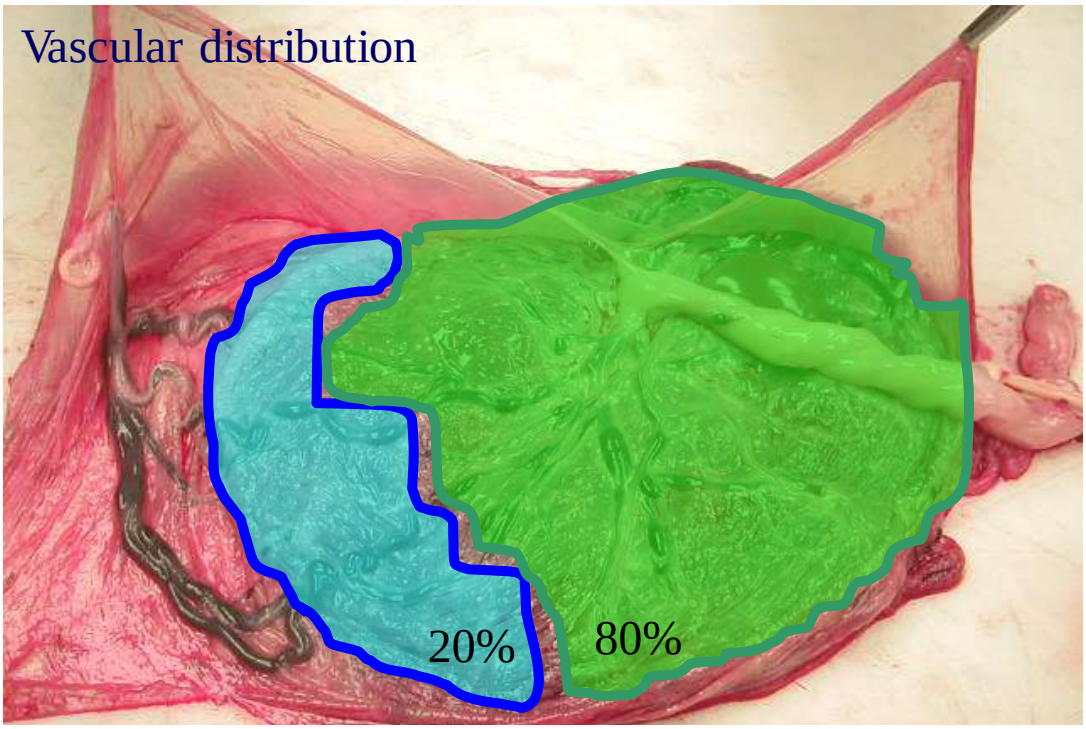
Vascular distribution

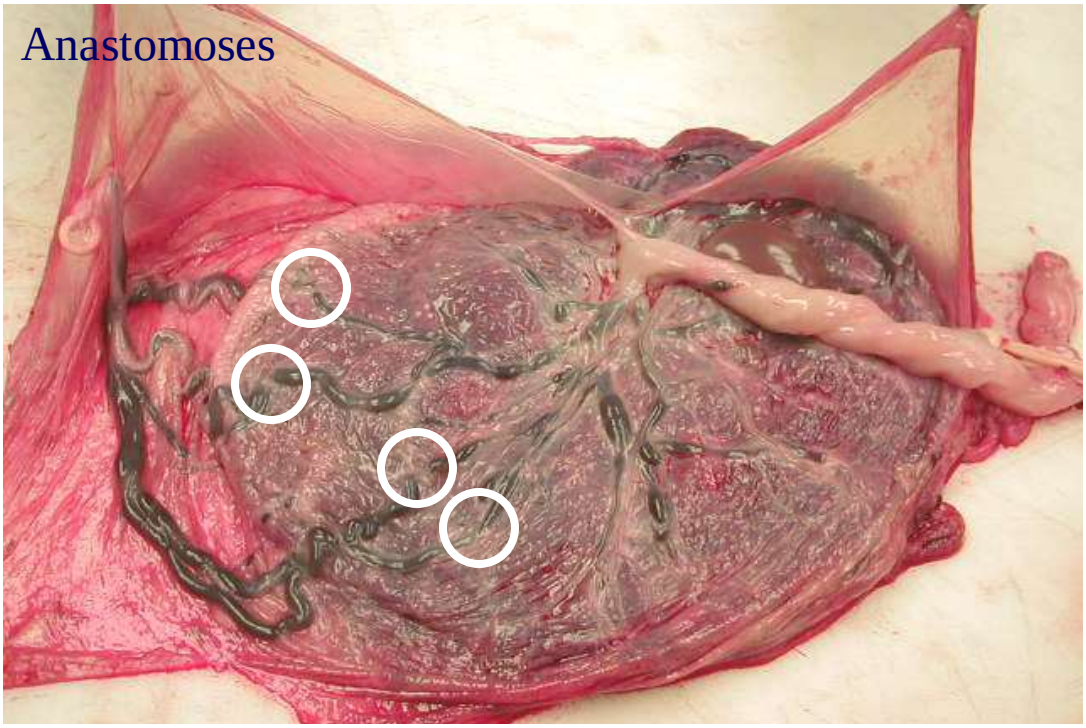


Vascular equator

Anastomoses

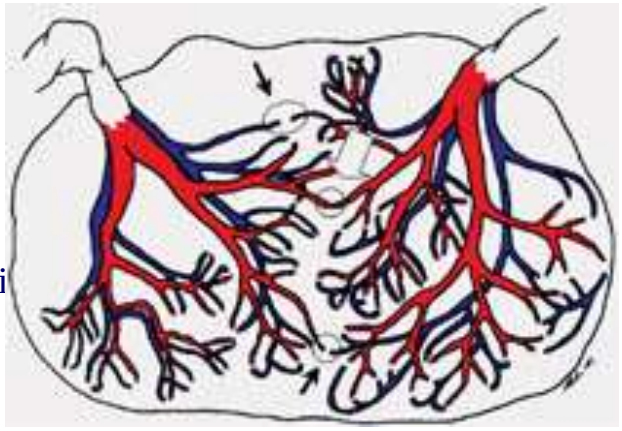
Vascular distribution





Anastomosis-types

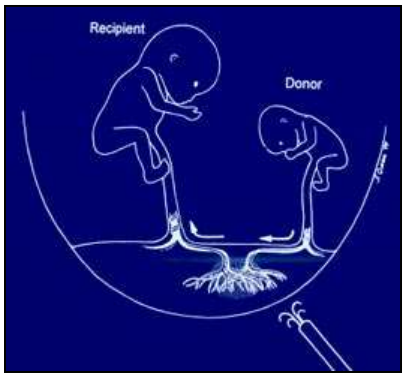
- Monoamniotic monochorial :
  - Arterio-arterial
  - Veno-venous
- Two way flow is possible

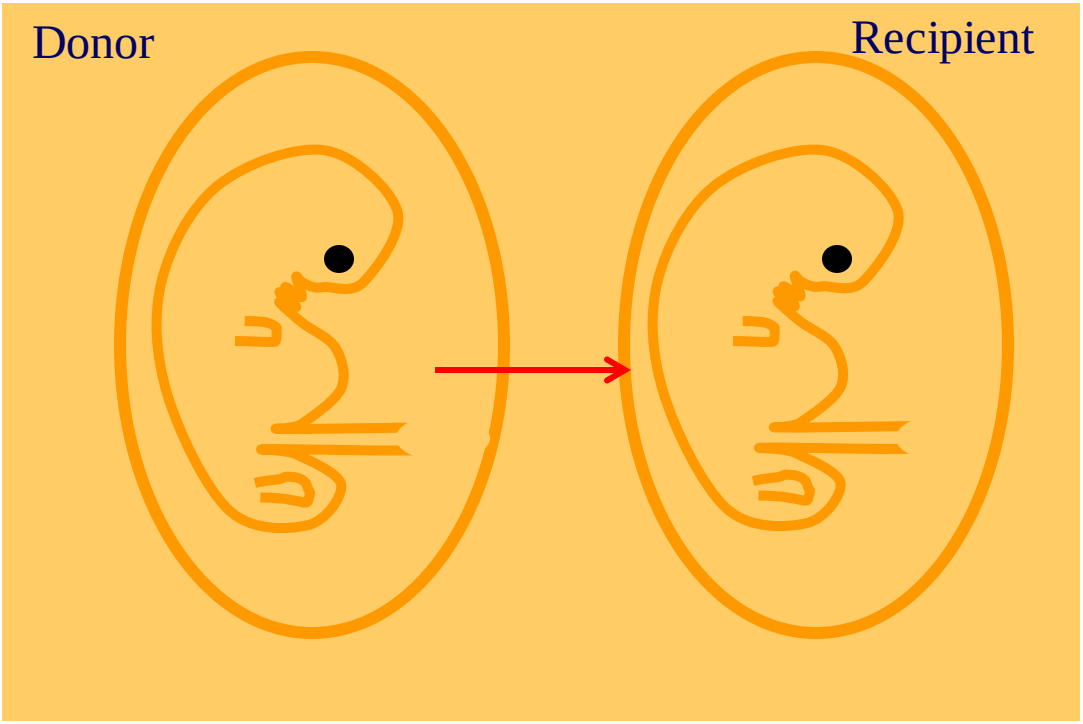


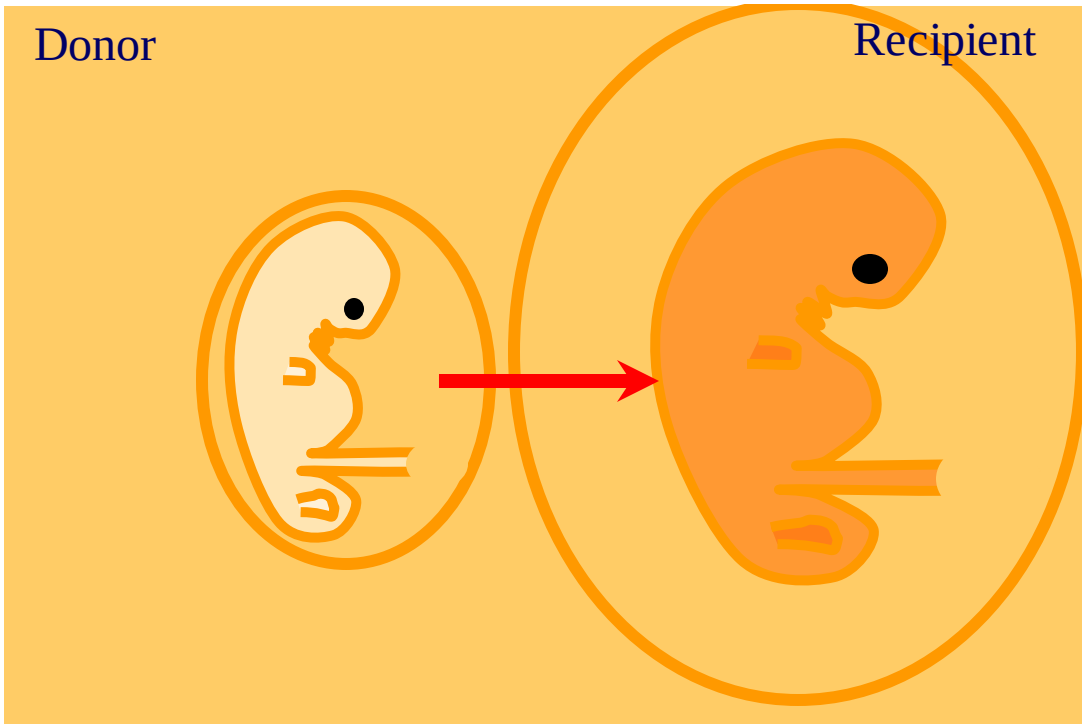
- Diamniotic monochori
  - Arterio-venous
- Only one way flow is possible

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



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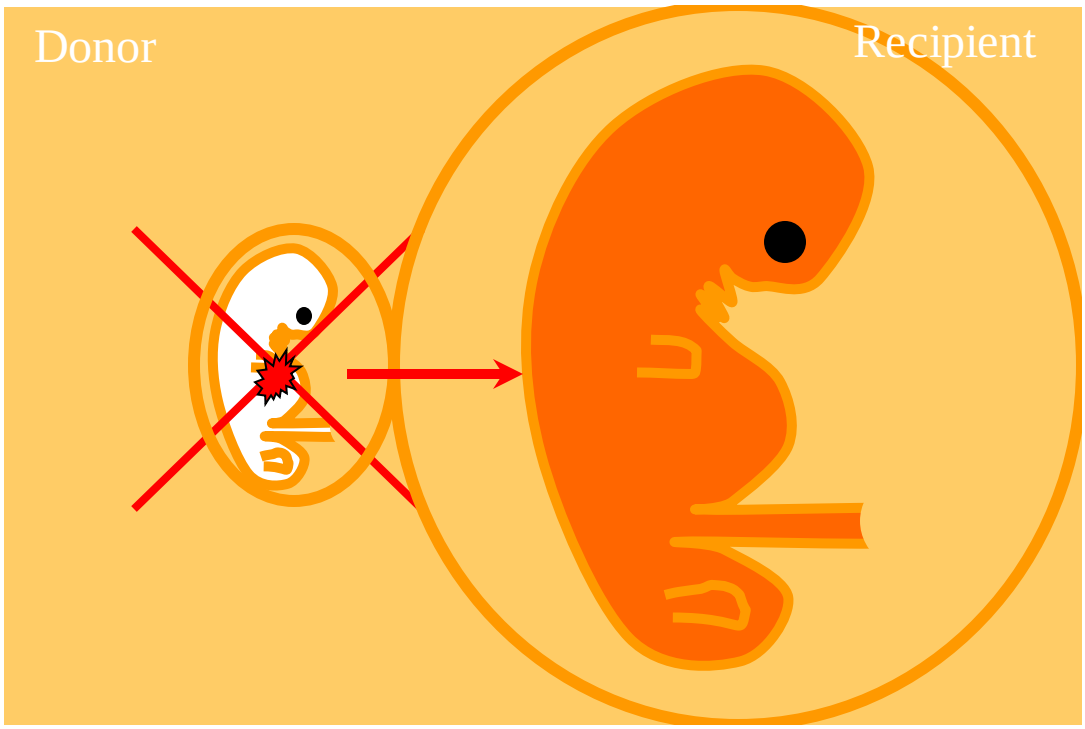
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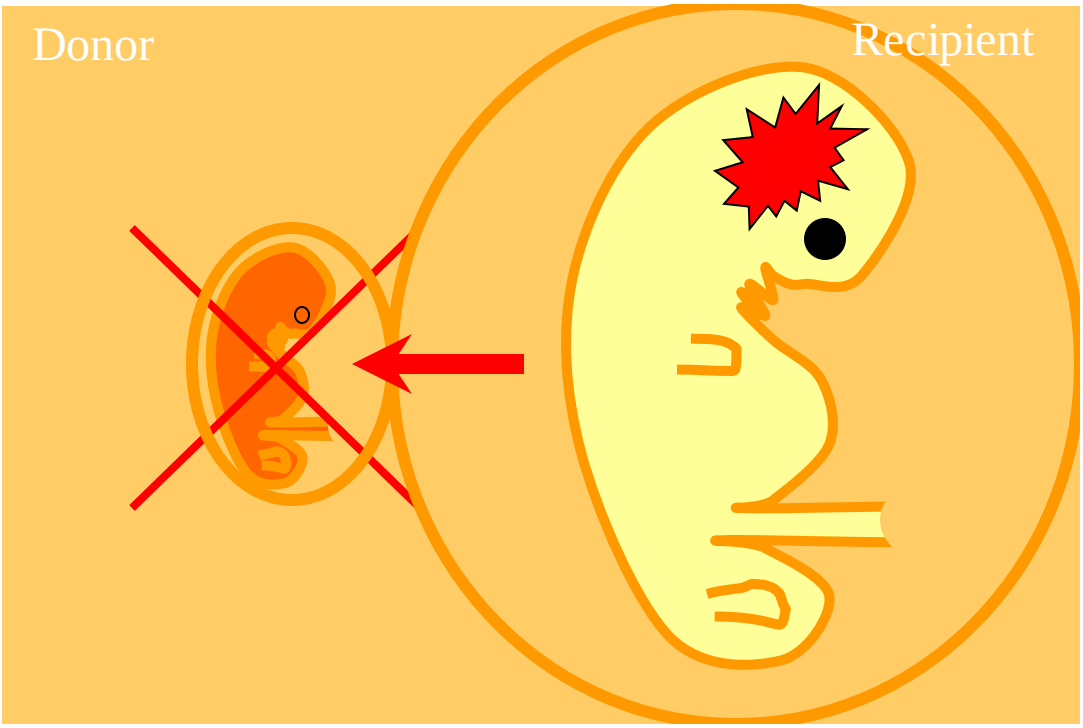
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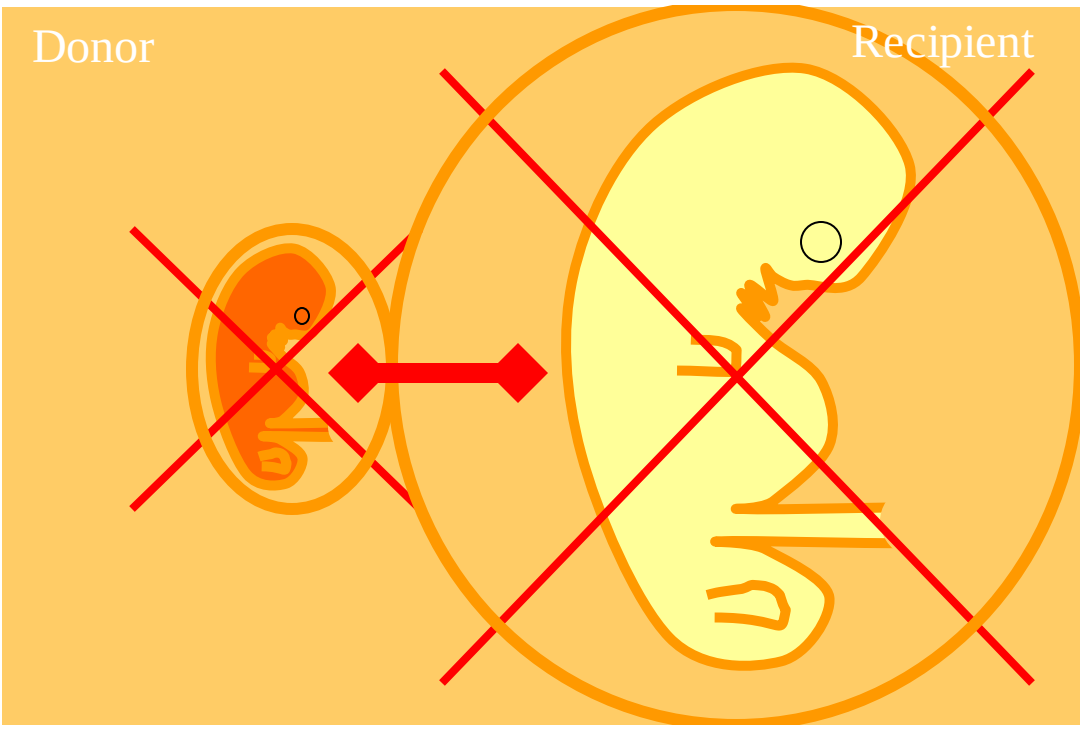
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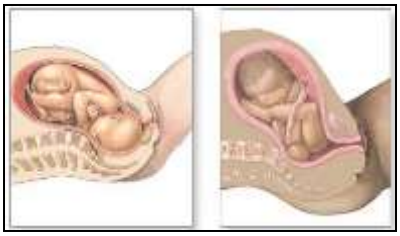
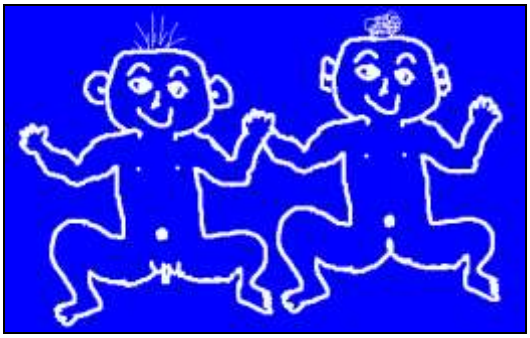
The process of birth

- First phase:
  - Foetus positioned into the birth canal
    - Abnormal presentation, size dyscrepancies
- 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:

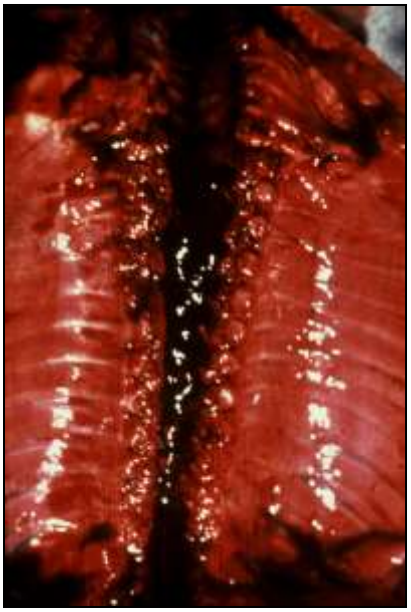
Scalp haemorrhage (vacuum extraction), subgaleal, subdural hematoma, intraspinal,

•Vertebral column haemorrhage

Visceral haemorrhages (eg. adrenal)

Intrapartum death:

Asphyxia during the second stage



Conditions affecting the newborn

Naeye classification

Placental disorders

- Amniotic fluid infection
- Abruptio placentae
- 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

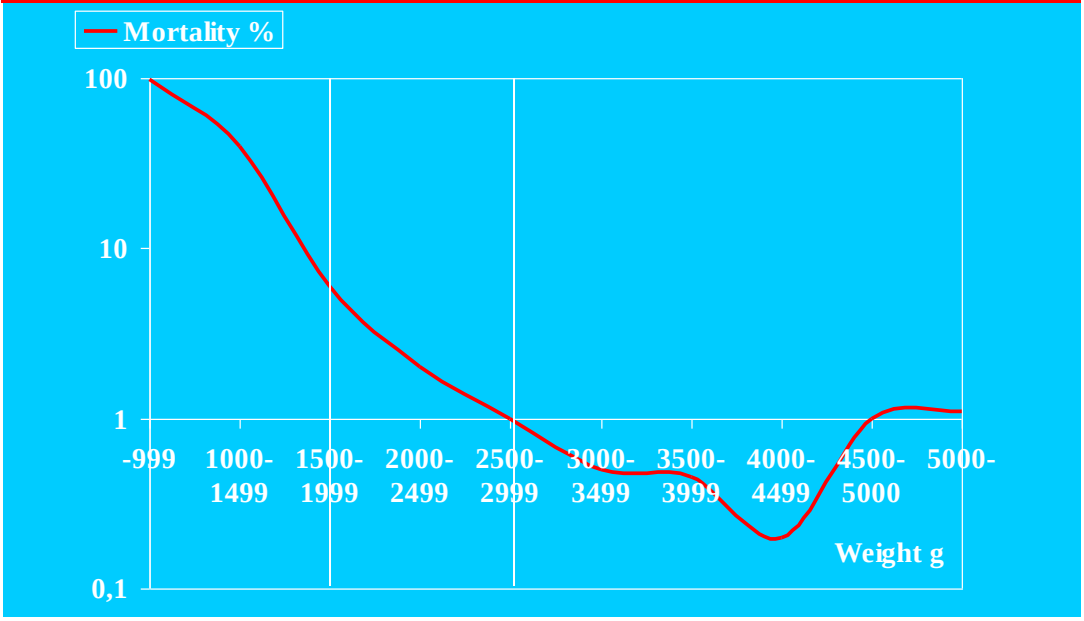
The neonate

- 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

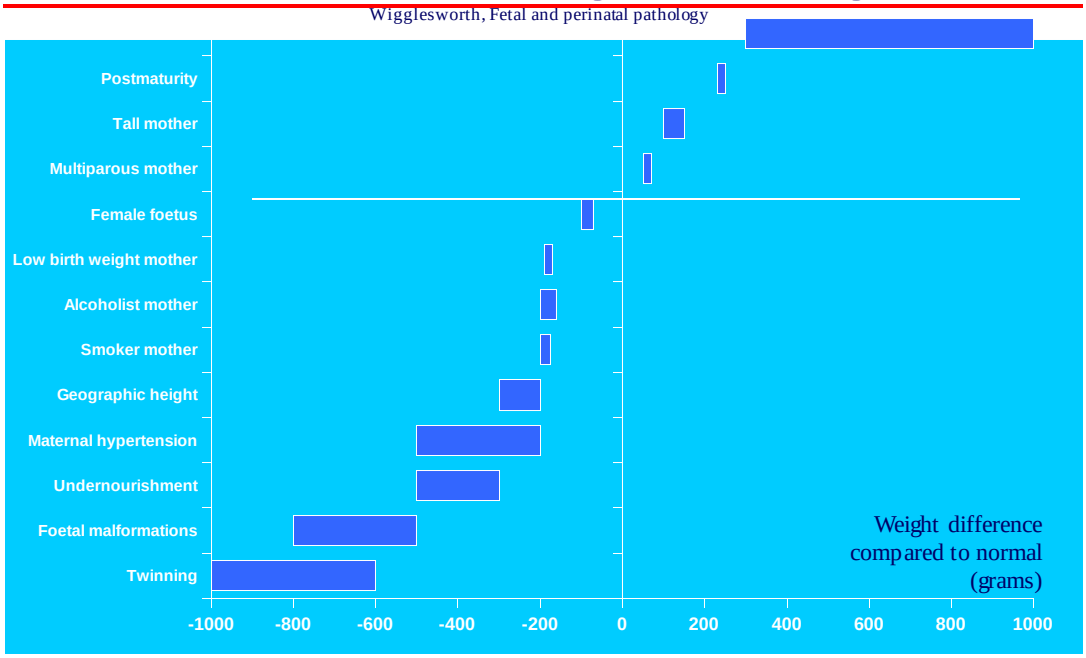
Low birth weight: Two groups of neonates are born weighing less than the normal minimum birth weight of 2,500 g (5½ lb)—those who are born prematurely (before the 37th week of gestation) and those who are **small for gestational age (SGA).** The premature neonate weighs an appropriate amount for his 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

Dési: Public Health (Népegészségtan)



Factors influencing birth weight

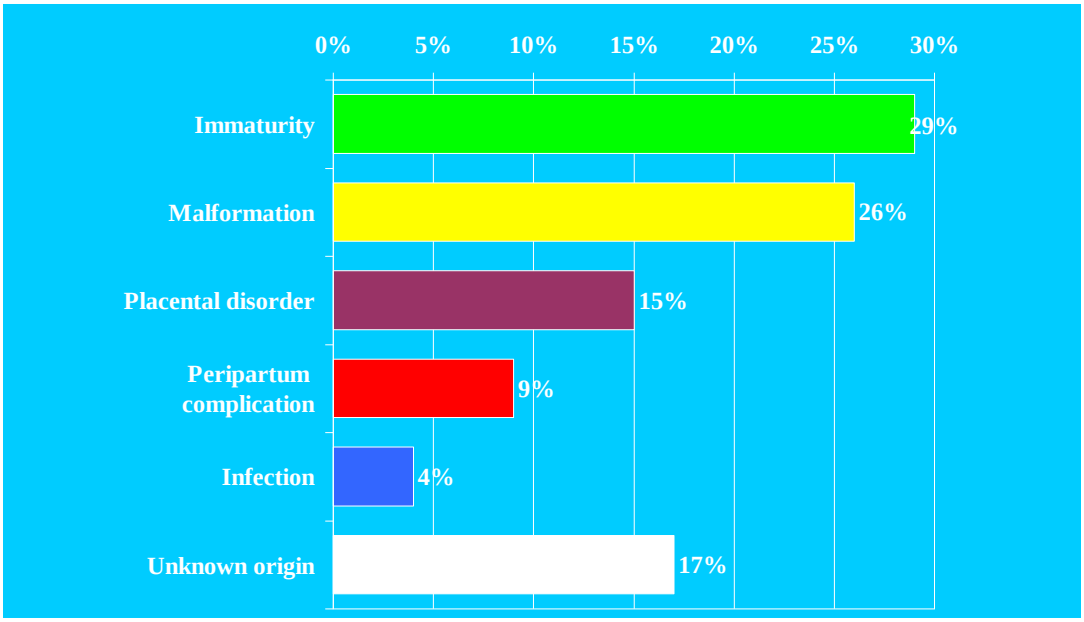


Because low birth weight may be associated with poorly developed body systems, particularly the respiratory system, your priority is to monitor the neonate's respiratory status. ***Be alert for signs of distress, such as apnea, grunting respirations, intercostal or xiphoid retractions, or a respiratory 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



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

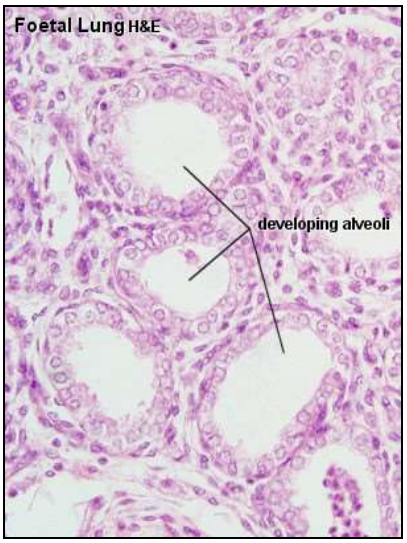
- **In the presence of hypoxia or acidosis (generally present in ductus-dependent lesions), the ductus may remain open for a longer period of time.**
- **As a result, these patients often present to the ED during the first 1-3 weeks of life.**
  - **i.e. as the ductus begins to close.**

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

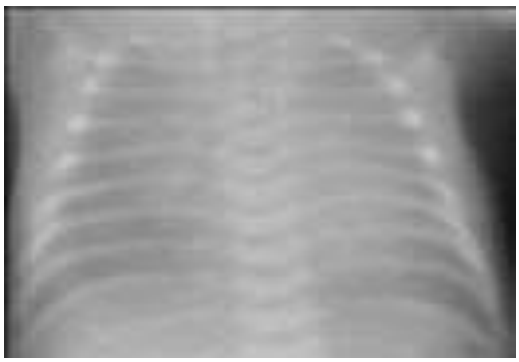
LUNG - Diseases of the premature neonate

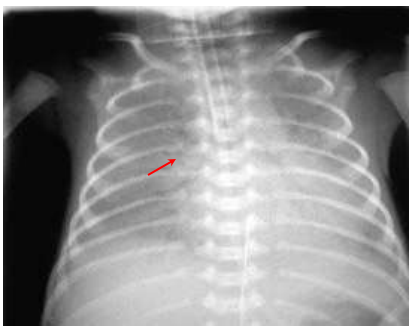
- **Respiratory:**
  - **IRDS (idiopathic respiratory distress syndrome), hyaline membrane disease**
  - **BPD (bronchopulmonary dysplasia)**
  - **Interstitial emphysema, pneumothorax**
  - **Pulmonary haemorrhage**
  - **Pneumonia, sepsis**

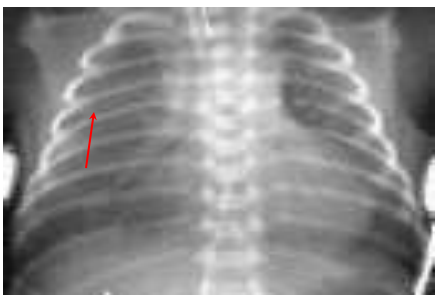


RDS

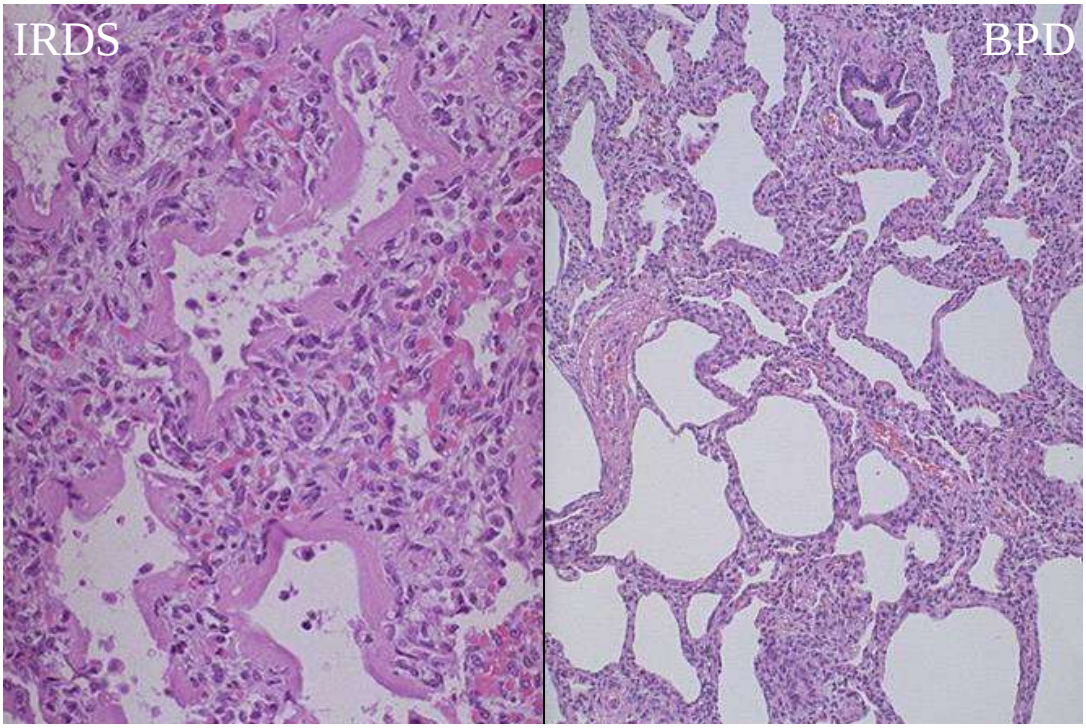
- Respiratory Distress Syndrome
- Immaturity of Lungs
- Need Surfactant
- Need Ventilation





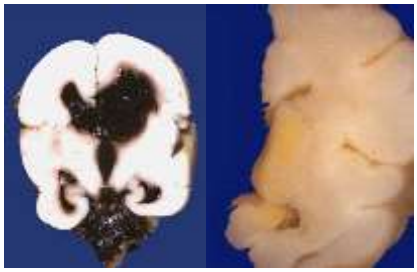


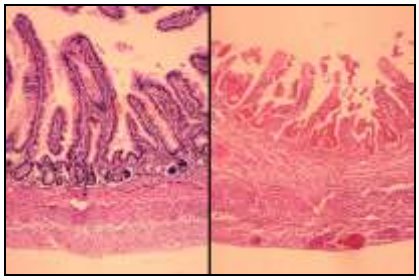
Reticugranular
(Ground Glass)
Air Bronchogram



Diseases of the premature neonate

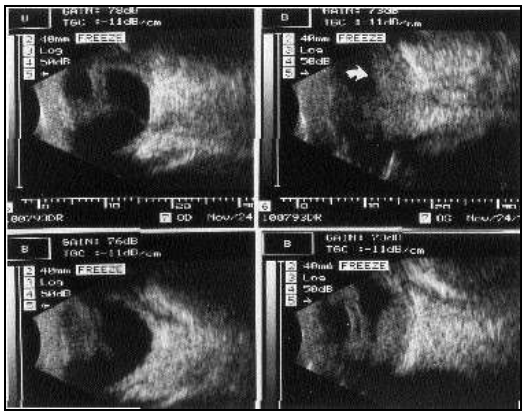
- Central nervous system:
  - Intraventricular haemorrhage (IVH)
  - Internal hydrocephalus
  - Kernicterus
- Intestinal:
  - Necrotizing enterocolitis (NEC)





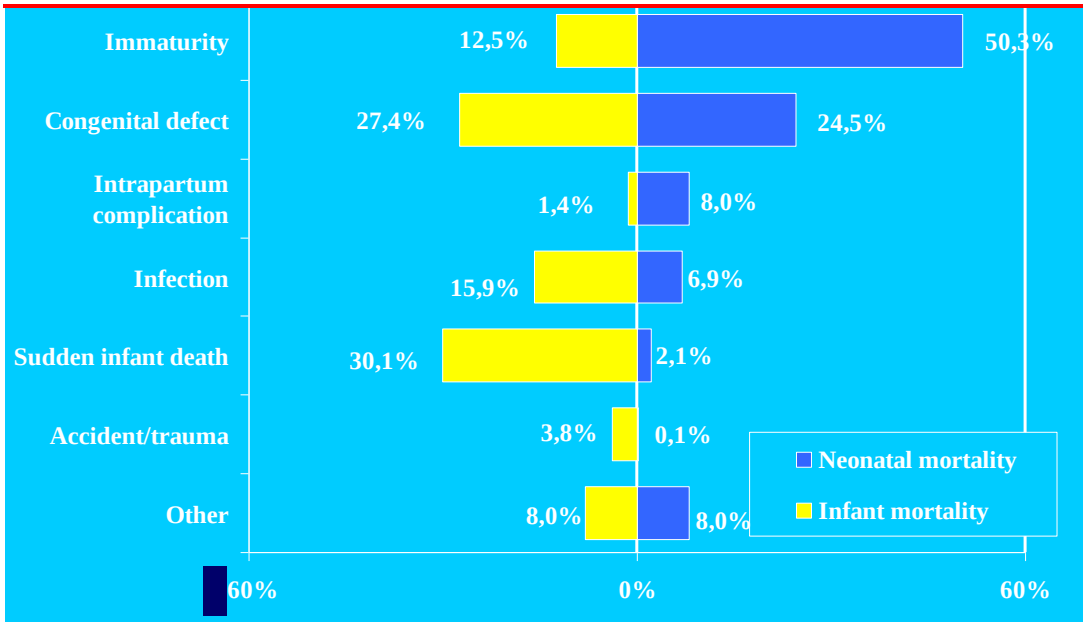
Diseases of the premature neonate

- Ocular
  - Retinopathy of prematures (ROP), retrolental fibroplasia
- Infection
  - Intrauterine contamination
  - Immature immune system
  - Iatrogenic infections



Neonatal and infant mortality

CESDI data

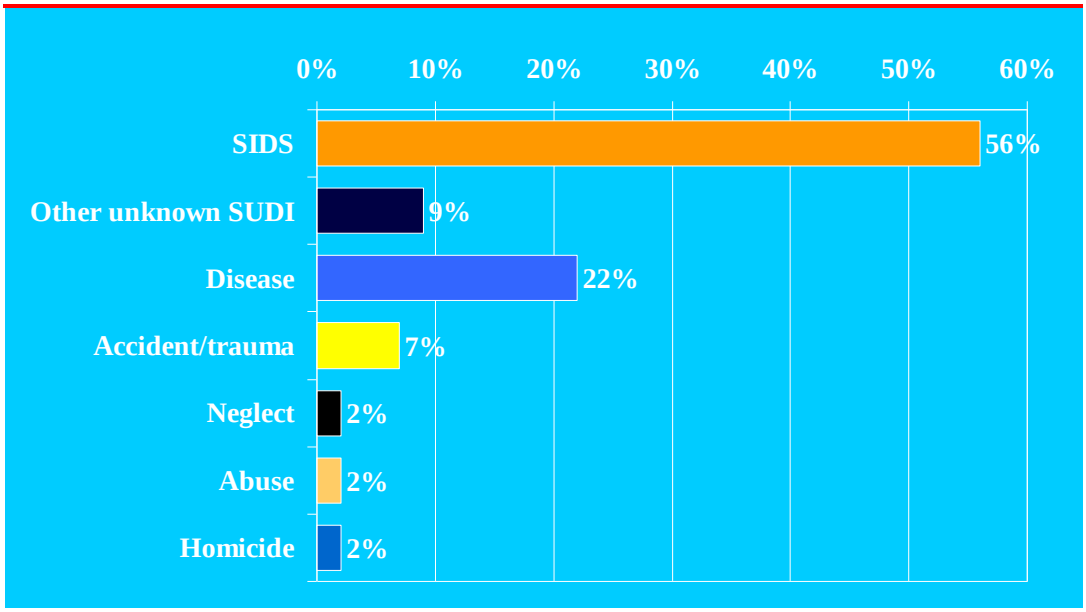


Investigation of SUDI

- 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

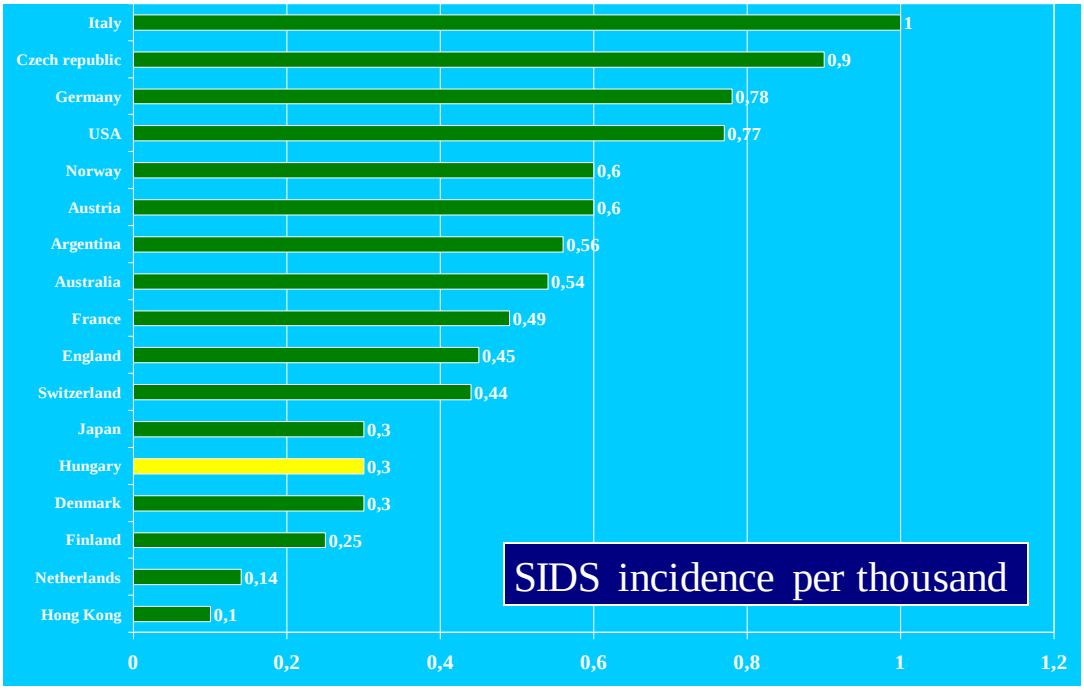
Causes of SUDI

Scandinavia 1990-2000



SIDS risk factors

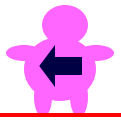
- Sociodemographic factors:
  - Family circumstances
  - Male infant
  - Winter period
- Pregnancy history
  - Multiparous mother
  - Low birth weight
  - Smoker mother, father
  - Maternal cocaine, opiate abuse
  - Alcohol abuser mother
- Factors after birth:
  - **Infections**
  - Passive smoking
  - **Sleep position – prone or side**
  - Bed-sharing
  - Soft sleep surface
  - Covering of head
  - Overheating



Prevention

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

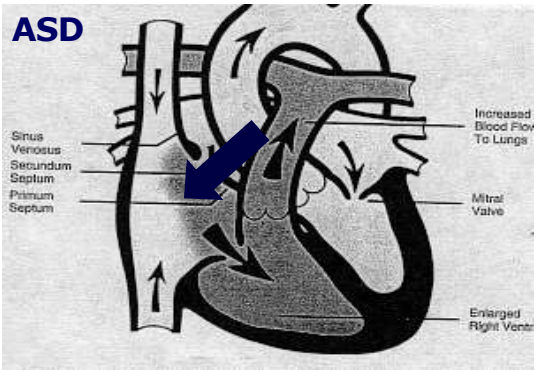
CHD- Pink Baby (L → R shunt)

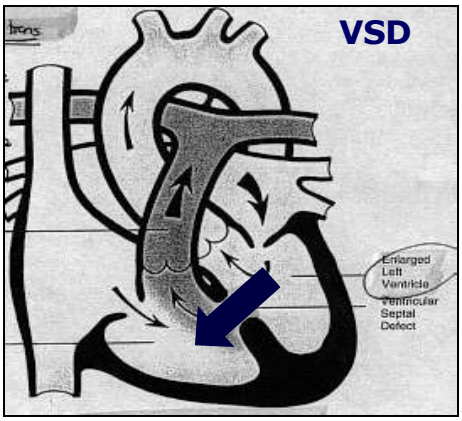


- L → R shunts cause chronic heart failure (CHF- congenital heart failure) and pulmonary hypertension.
- This leads to RV enlargement, RV failure, and cor pulmonale.
- These babies present with CHF and respiratory distress.
  - They are not typically cyanotic.

Pink Baby (L → R shunt)

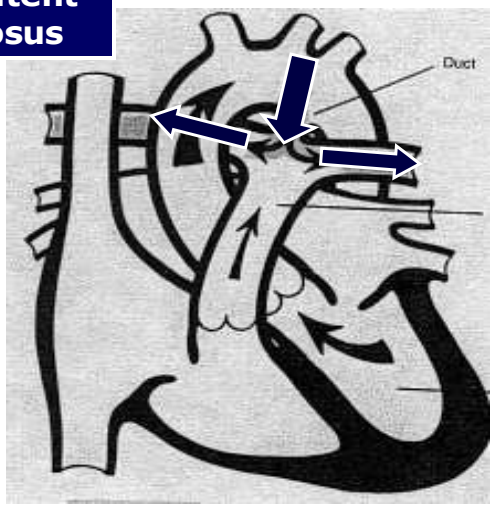
- These lesions include (among others) ASD's, VSD's, and persistently patent ductus arteriosus.





Pink Baby (L → R shunt)

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

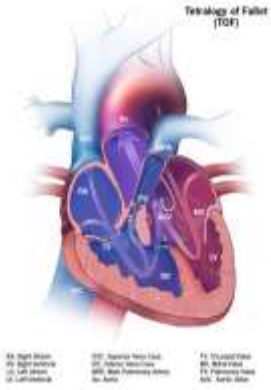
Blue Baby (R → L shunt)

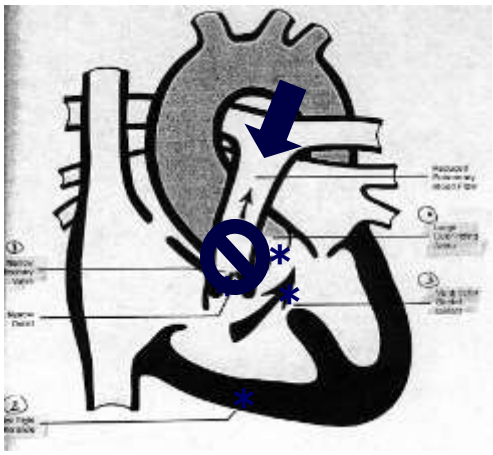
- R → L shunts cause hypoxia and central cyanosis.
- Neither hypoxia or cyanosis tend to improve with 100% oxygen.
- R → L lesions include (among others):
  - Tetralogy of Fallot (TOF)
  - Transposition of the Great Arteries (TGA)

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...

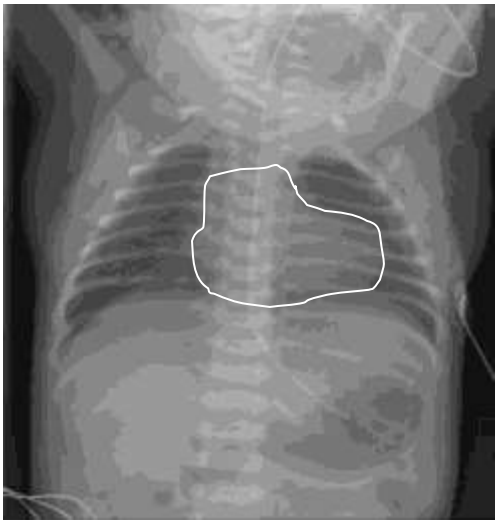




bloodflow to the lungs may be highly ductus-dependent.

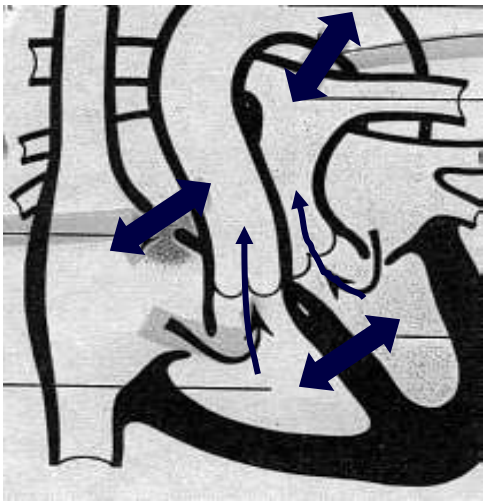
Tetralogy of Fallot

- The classic X-Ray finding in TOF is the boot-shaped heart.
- Pulmonary vasculature is typically decreased.



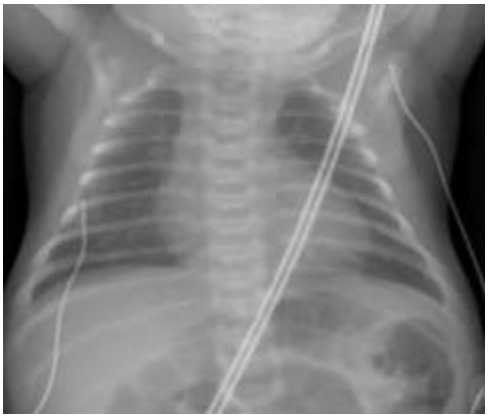
Transposition of the Great Arteries

- 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

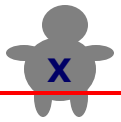
- The CXR (chest X-Ray) findings in TGA are typically less dramatic than in TOF.
- Pulmonary vasculature is typically increased.



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 (PGE_1) 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

- PGE_1 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– as adverse-effects of PGE_1 can include:

  - fever
  - flushing
  - diarrhea
  - periodic apnea (be ready to intubate)