The most frequent congenital defects in childhood

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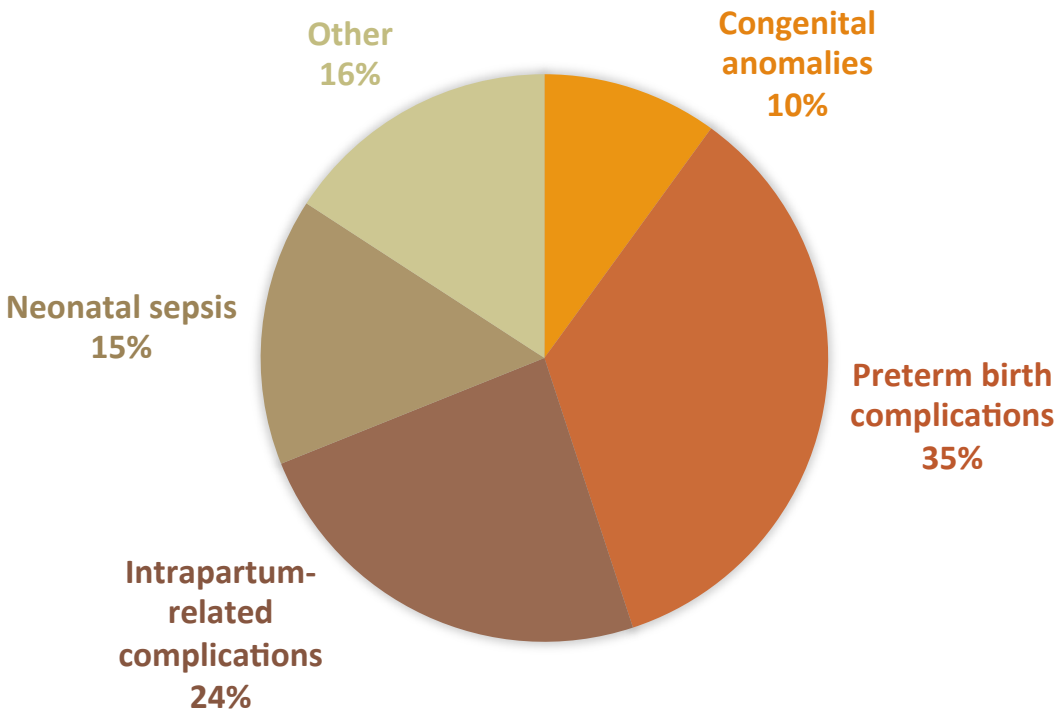
Congenital defects

1. Congenital defects:
   - structural or functional anomalies which are present at the time of birth and often before birth
   - also known as birth defects, congenital disorders or congenital malformations
   - 2-3% of newborn (4-6% by age 5)
2. Congenital anomalies can result in long-term disability, which may have significant impacts on individuals, families, health-care systems and societies.
3. Congenital anomalies affect an estimated 1 in 33 infants and result in approximately, 3.2 million birth defect-related disabilities every year

Congenital defects

1. Congenital disorders vary widely in causation and abnormalities
2. Any substance that causes birth defects is known as a teratogen
3. Some disorders can be detected before birth through prenatal diagnosis (screening)
4. Most common severe congenital anomalies are heart defects, neural tube defects and Down syndrome

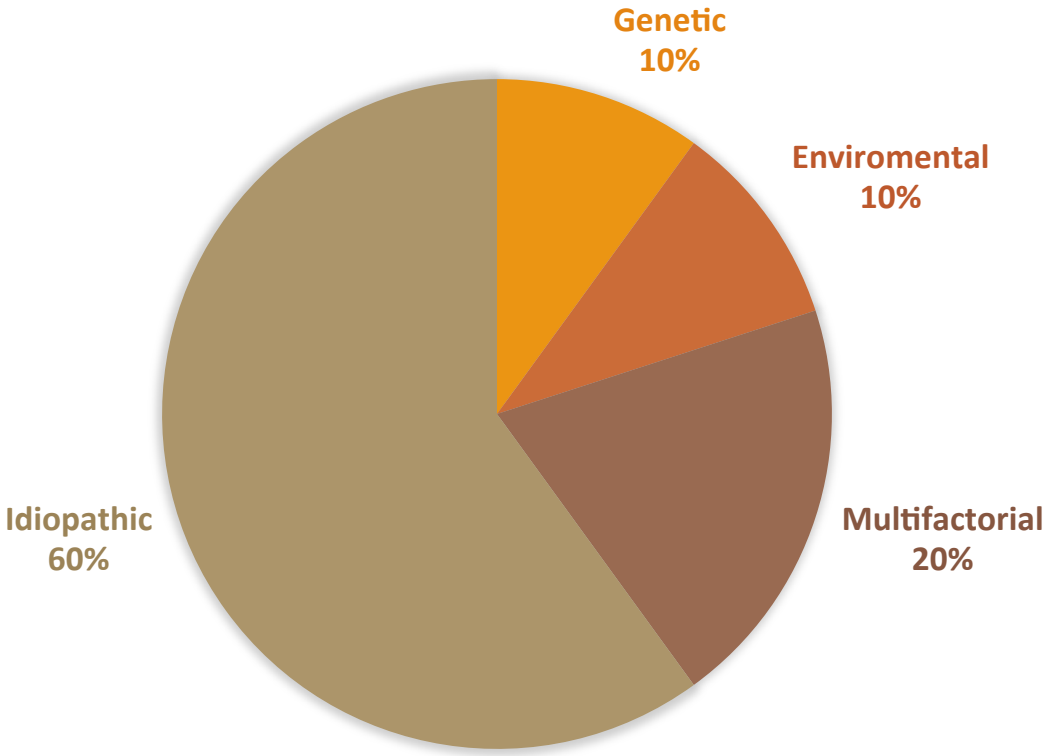
Causes of deaths during neonatal period in 2013 worldwide



Etiology

Genetic	• chromosomal abnormalities • mutation de novo, mutation inherited • interaction of genetic and environmental factors
Enviromental	• Maternal exposure to: pesticides, medications, alcohol, tobacco, psychoactive substances, certain chemicals, high doses of vitamin A during the early pregnancy, high doses of radiation
Infectious	• TORCH (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Syphillis) • Varicella • HIV
Socioeconomical	• congenital anomalies are more frequent among resource constrained families and countries • advanced maternal age
Maternal nutrition status	• Iodine deficiency • folate insufficiency • diabetes mellitus
Idiopathic	•In 40-60% of all birth defects cause is unknown

Causes of congenital defects



Classification of congenital defects

Primary abnormality: defect in the structure of an organ or a part of an organ that can be traced back to an anomaly in its development

- Gene aberrations- 7.5% of congenital abnormalities.
  - Monogenetic mutations or polygenetic mutations are involved that can be further inherited in accordance with Mendel's laws.
- Chromosomal aberrations- 0,5 % of congenital abnormalities
  - Two kinds: structural and quantity aberrations
- Multifactorial anomalies- cause is by genetic and enviromental factors
  - Abnormalities of the neural tube, cleft palates, cardiac-circulation-disorders, dysplasia of the hips

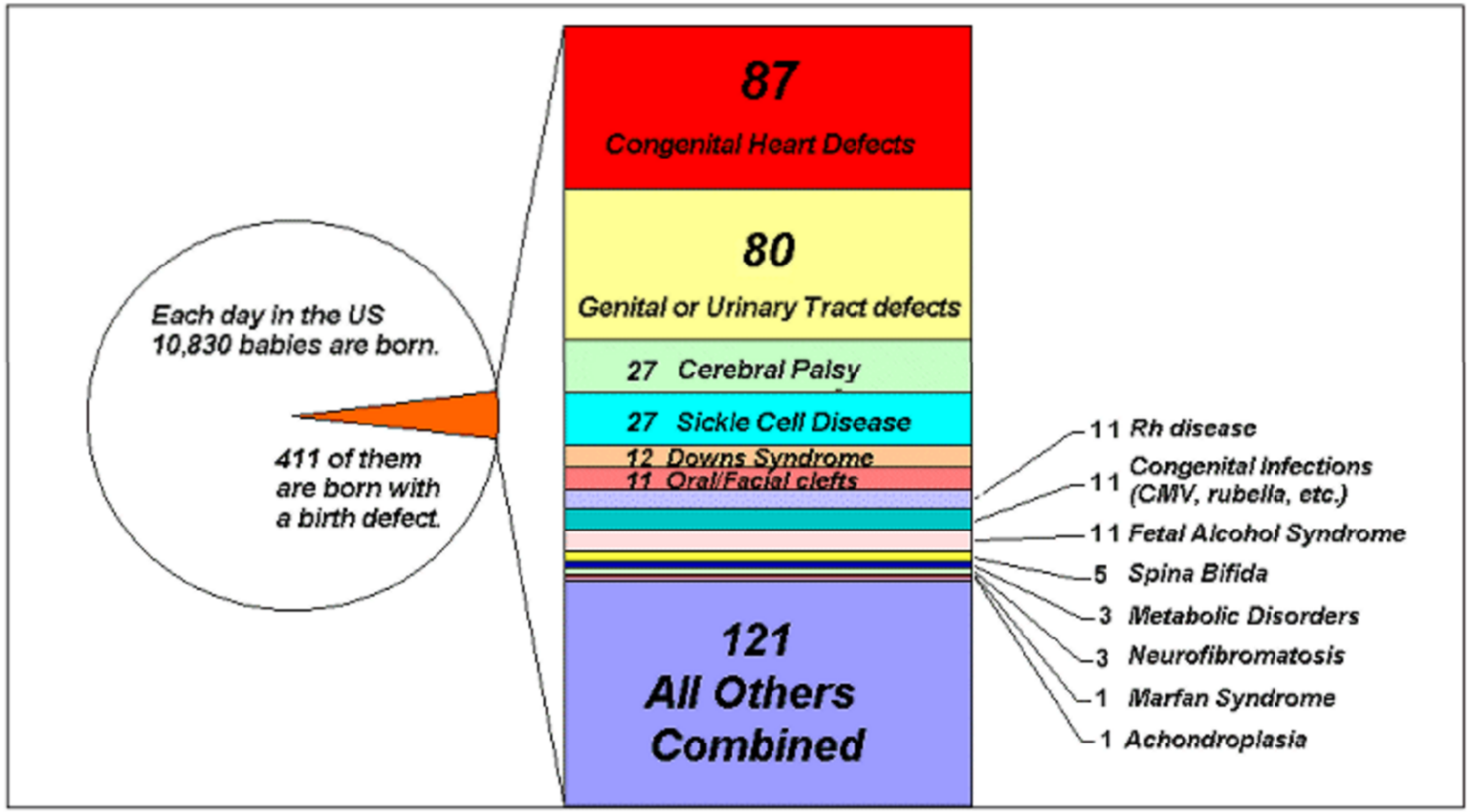
Secondary abnormality („disruption"): interruption of the normal development of an organ that can be traced back to outer influences.

- Caused by teratogenic agents (infection - TORCH, chemical substance- drugs- thalidomide, warfarin, chloroquine, lithium, ionizing radiation) or a trauma (amniotic bands, which led to an amputation)
- Congenital abnormality is not always inherited

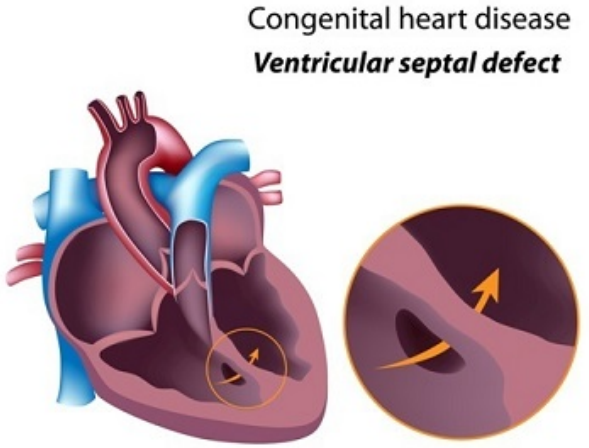
Classification of congenital defects

- **Deformation**: anomalies that occur due to outer mechanical effects on existing normal organs or structures, often involve the musculoskeletal system and may be reversible postnatally (eg. clubfeet due to compression in the amniotic cavity)
- **Dysplasia**: abnormal organization of the cells in a tissue (e.g. osteogenesis imperfecta), numerous dysplasias are genetically caused (e.g. achondroplasia).
- **Agenesia**: the absence of an organ due to a development that failed to happen during the embryonic period
- **Sequence**: a pattern of cascade anomalities explained by a single localized initiating event with secondary defects in other organs (e.g. Potter's sequence, Pierre-Robin sequence)
- **Syndrome**: a group of anomalies occuring together with a specific common etiology (Down syndrome, Turner syndorme)

Congenital defects- frequency



Congenital heart defects



- 7-10 per 1000 births
- Early detection- screening by fetal USG
- They are typically arise in the 3rd–8th week of gestation.
- In neonates and children with CHD, **15%** will have more than one cardiac abnormality and **15%** will have another extra-cardiac abnormality.
- VSD - majority of all acyanotic heart defects, TOF - majority of all cyanotic heart defects
- There is often no obvious aetiology; most would appear to be multifactorial with both genetic and environmental influences:
  - Infection-> rubella
  - Maternal DM, drugs/medications, alcohol
  - Genetic factors: Marfan syndrome, trisomy 21, trisomy 18, Turner syndrome

Signs and symptoms

Infants

- Tachypnea
- Failure to thrive
- HR > 200 bpm
- Heart murmur
- Congestive heart failure
- Cyanosis

Children

- Dyspnea
- Slow physical development
- Decreased exercise tolerance
- Heart murmur
- Congestive heart failure
- Cyanosis.
- Clubbing of digits
- Hypertension

Congenital heart defects

ACYANOTIC HEART DISEASES

Atrial septal defect

Ventricular septal defect

Patent ductus arteriosus

Aorticopulmonary fenestration

Aortic stenosis

Pulmonic stenosis

Coarctation of aorta

CYANOTIC HEART DISEASES

Tetrology of Fallot

Eisenmenger's syndrome

Ebstein's anomaly

Tricuspid atresia

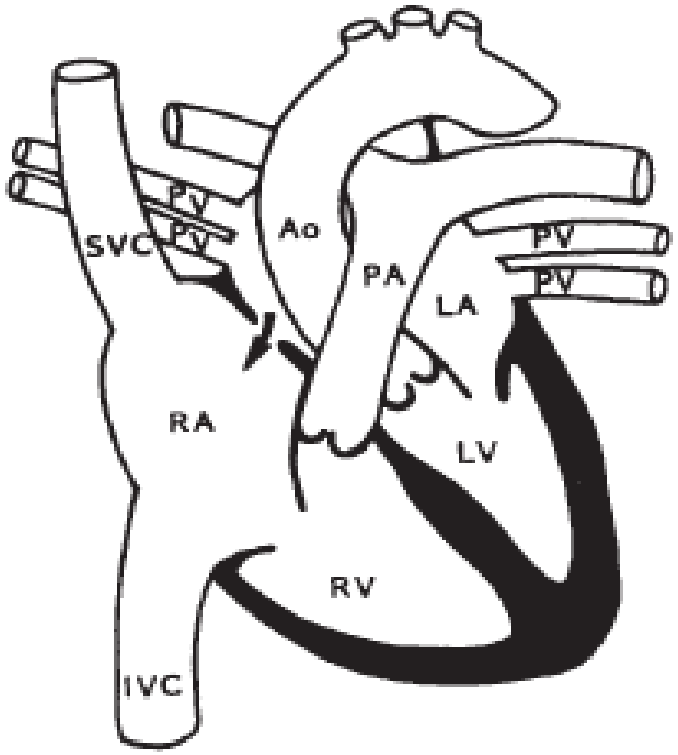
Transposition of great arteries

Truncus arteriosus

Hypoplastic left heart syndrome

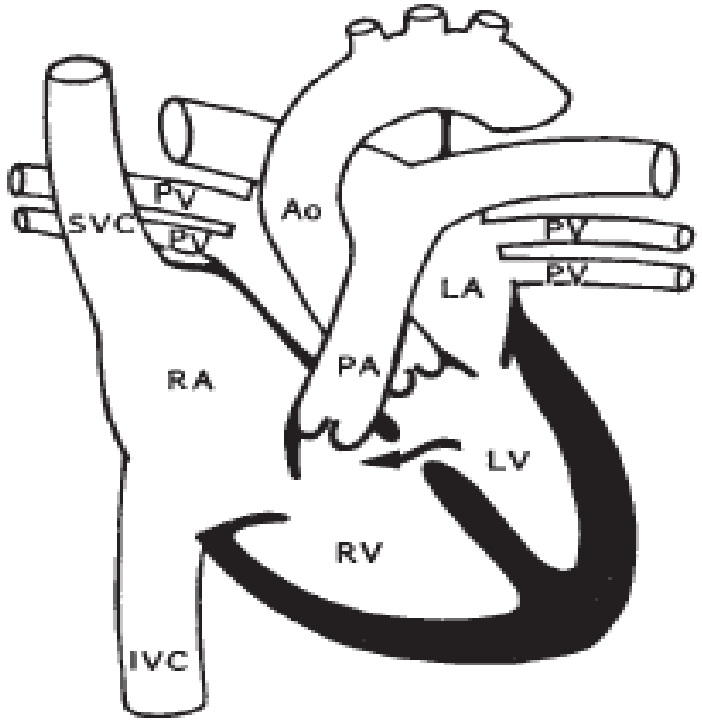
Atrium septal defect, ASD

- 1/3 of the congenital heart disease detected in adults – increased incidence in females
- 3 types:
  1. ostium primum ASD
  2. secundum ASD,
  3. coronary sinus ASD
- Secundum ASD – 75% of all the ASD cases
- Direction and magnitude of shunt depends on the size of defect and compliance of ventricle
- Murmur detected usually by 6-8 weeks, heard in 2nd left ICS



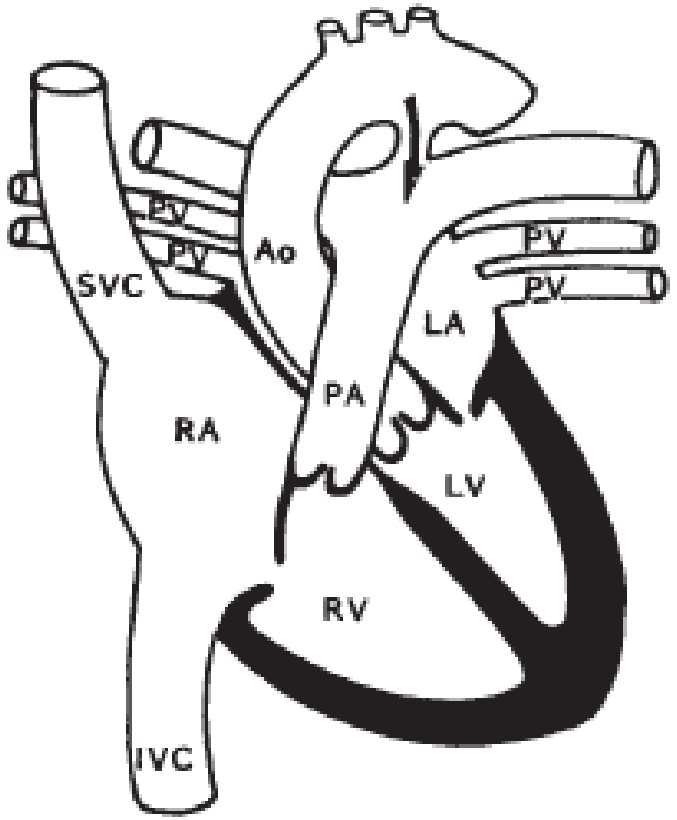
Ventricular septal defect, VSD

- Most common congenital cardiac anomaly in infants and children
- These account for 20-30% of congenital heart disease and affect approximately 2 in 1000 live births
- Accounts for most common congenital cardiac anomaly in adults excluding a bicuspid aortic valve
- Many of them spontaneously resolve by 2yrs of age
- Holosystolic murmur – loudest at the lower left sternal border



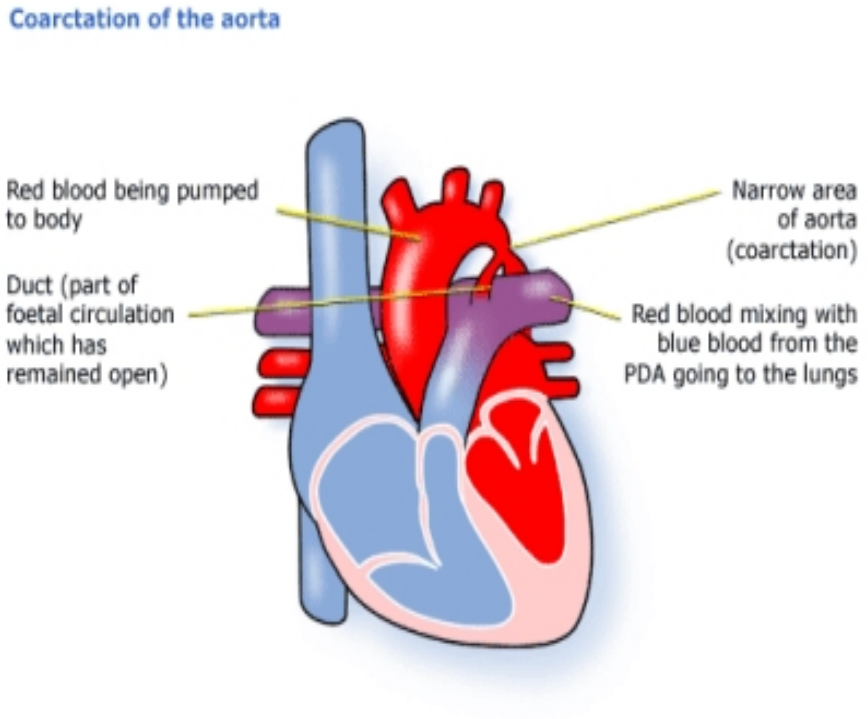
Patent ductus arteriosus, PDA

- Accounts for 8-12% of congenital heart disease.
- The ductus arteriosus, a normal fetal communication, facilitates the transfer of oxygenated blood from the pulmonary artery to the aorta shunting blood away from the lungs
- Normally, functional closure of the ductus occurs within a few hours of birth; it is abnormal if it persists beyond the neonatal period; usually seen with preterm infants



Coarctation of the aorta

- This accounts for 6-7% of congenital heart disease
- It is a haemodynamically significant narrowing of the aorta, usually in the descending aorta just distal to the left subclavian artery, around the area of the ductus arteriosus
- Postductal – extends just distal to the left subclavian artery at the site of aortic ductal attachment (ligamentum arteriosum) – manifests in young adults
- Preductal – less common – coarctation is just proximal to the left subclavian artery, diagnosed in infants.
- Children with coarctation are usually male and, if it occurs in females, it can be Turner syndrome

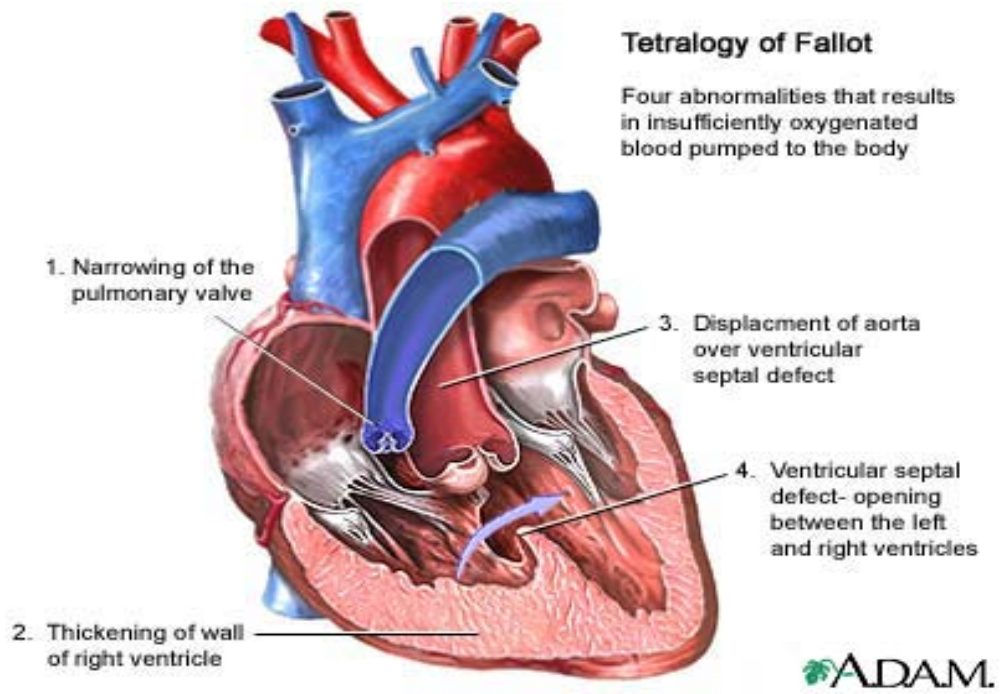


Fallot tetralogy

This is the most common cyanotic congenital heart disease and accounts for about 4-6% of all congenital heart diseases.

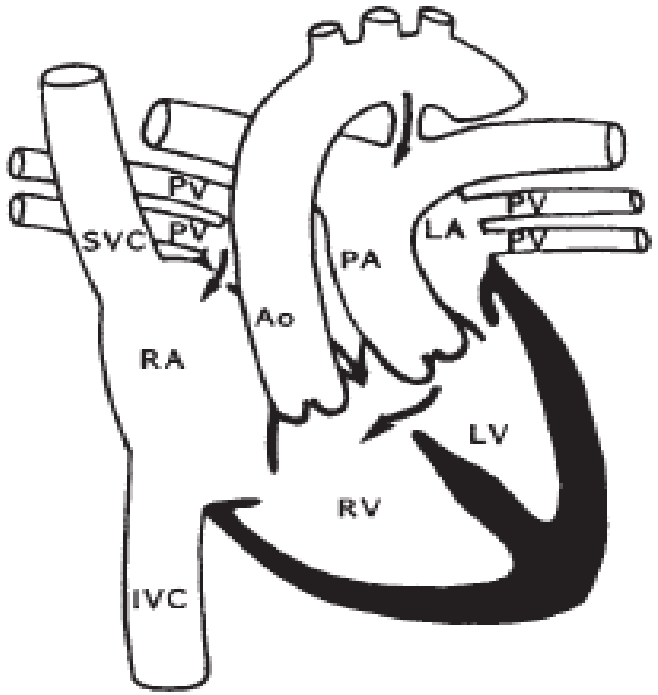
The four intracardiac lesions originally are:

1. Pulmonary stenosis
2. Right ventricular hypertrophy
3. VSD
4. Overriding aorta

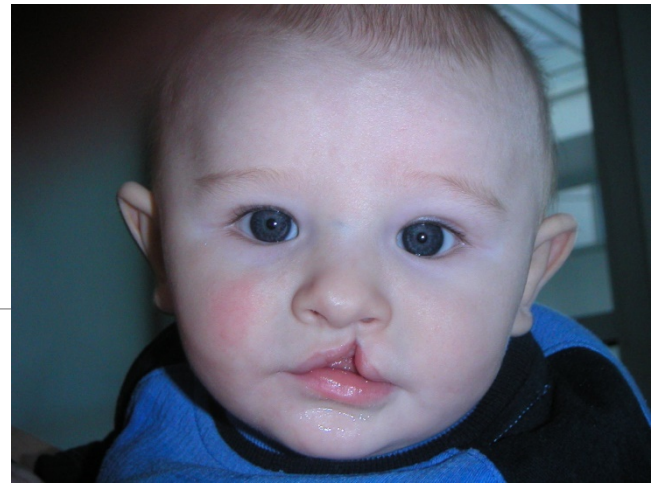


Transposition of great arteries

- 2.5-5% of all congenital heart disease
- The most common cause of cyanosis from a congenital cardiac defect discovered in the new-born period.
- Survival is possible only when there is communication between the circulations in the form of ASD, VSD or PDA.



Congenital defects of the face



- Includes:
  - Cleft lip and palate
  - Developmental abnormalities of the teeth
- Cleft lip, alveolus, hard and soft palate are the most common congenital abnormalities of the orofacial structures
- Cleft lip and palate is 1 in 600 live births. Isolated cleft palate is 1 in 1000 live births.
- The typical distribution of cleft types is:
  - Cleft lip alone 15%
  - Cleft lip and palate 45%
  - Isolated cleft palate 40%
- Cleft lip palate predominates in male, cleft lip alone more in females
- In unilateral cleft lip, the deformity affects left side in 60% of cases.

Etiology

Genetic predisposition

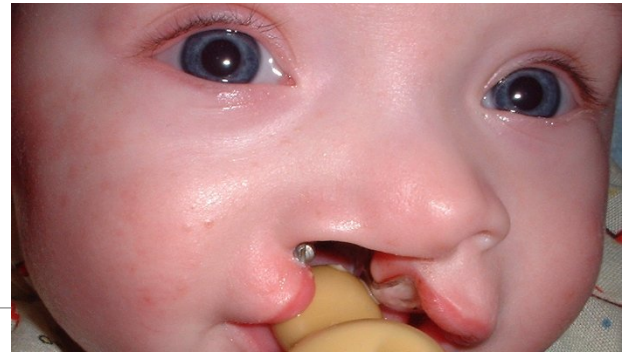
- Occurence of cleft lip and palate in 1st degree relatives increases the risk to 1 in 25 cases
- Oral clefts have been linked to genes located on more than several chromosomes including 1, 2, 4, 6, and 19

Environmental factors:

- Maternal epilepsy
- Drugs: steroids, phenytoin, diazepam
- Maternal folic acid deficiency
- Ingest large quantities of Vit A

Associated with syndromes (mostly isolated cleft palate)

- Pierre Robin sequence
- Apert syndrome



Complications

Hearing

- Higher incidence of sensorineural hearing loss and conductive hearing loss
- Regular hearing tests should be performed before 12 months of age

Speech:

- Velopharyngeal incompetence
- Articulation problems
- Speech problems
- Eating problems

Dental:

- Hypodontia, hyperdontia, delayed eruption of teeth

Management include dietary advice, fluoride supplements, and fissure sealants.

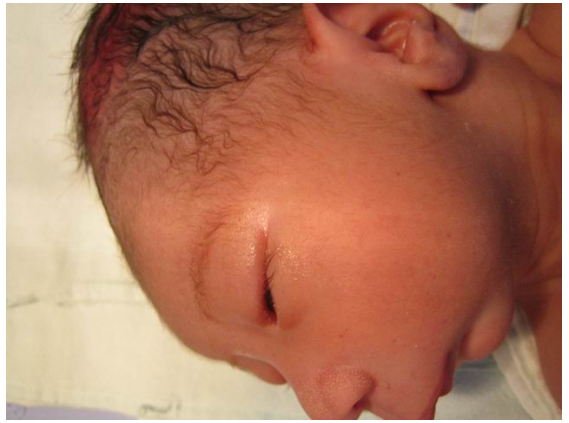
Pierre-Robin Sequence

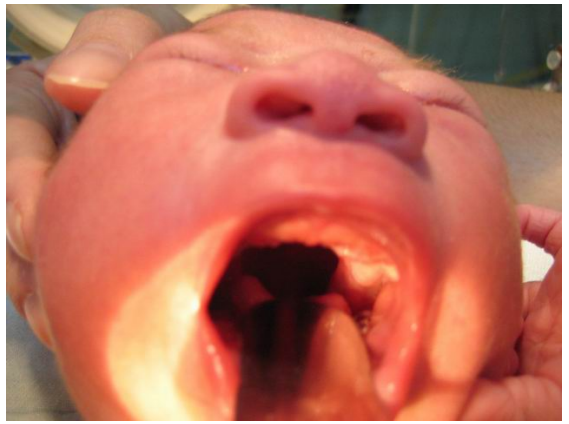
Triad of:

- Cleft palate
- Retrognathia (abnormal positioning of the jaw or maxilla)
- Glossoptosis (airway obstruction caused by backwards displacement of the tongue base)

Pathology: due to retrognathia which prevents descent of the tongue into the oral cavity; prevents secondary palate fusion

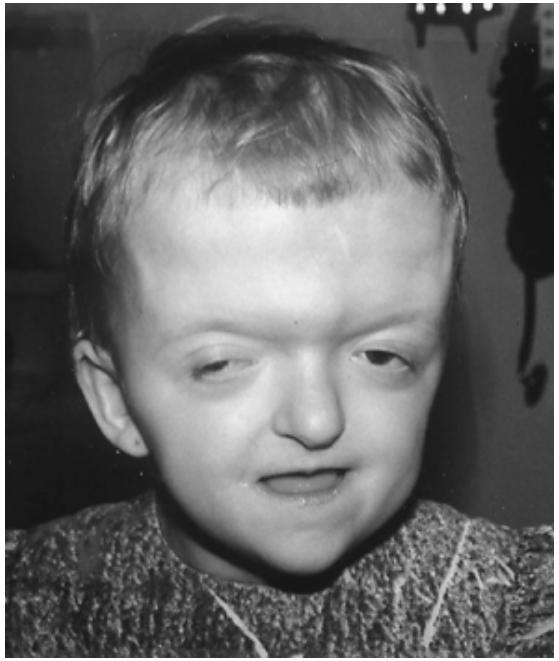
Associated with a syndrome in 50-80% of cases, most commonly Stickler syndorme, velocardiofacial syndrome





Apert syndrome (acrocephalosyndactyly)

- Autosomal dominant, most cases due to spontaneous mutation
- Common findings:
  - Craniosynostosis (pre-mature fusion of the cranial sutures)
  - Severe symmetrical syndactyly
  - Low-set ears
  - Cognitive function normal to severe mental retardation
  - Eyes: down-slanting palpebrael fissures, hypertelorism, exophthalmos
  - Midface hypoplasia
  - Mandibular prognathism
  - Possible cleft palate
  - Nose: Parrot-beaked nose, possible Choanal Atresia
  - Syndactyly and cervical fusion



Developmental abnormalities of the teeth

Anodontia a rare genetic disorder characterized by the congenital absence of all primary or permanent teeth.

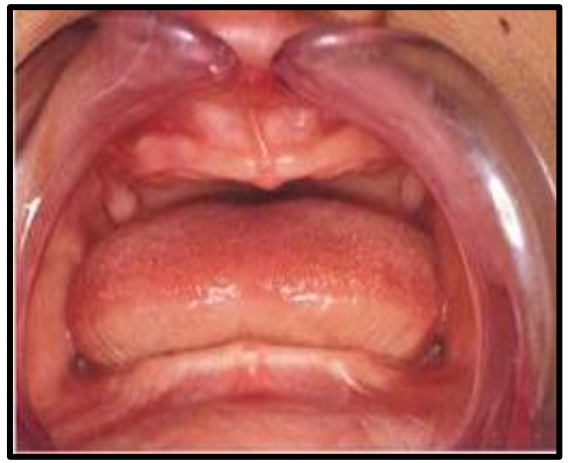
Partial anodontia (hypodontia) absence of one or more teeth because of absence of their primordium, which is seldom associated with other anomalies.

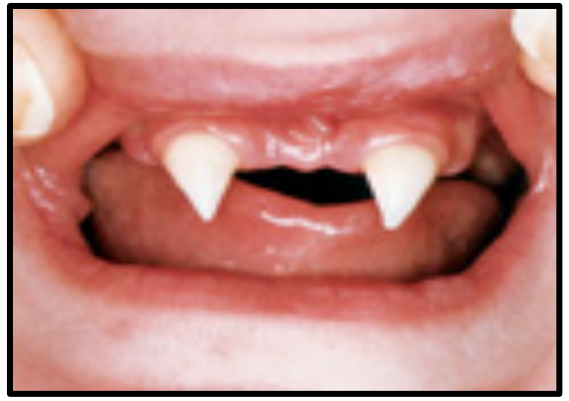
Most frequent absent teeth:

- Third molar (wisdom teeth)
- 2nd premolars
- Maxillary lateral incisor teeth

Associated with:

- Ectodermal dysplasia
- Down syndrome
- Cleft lip and palate



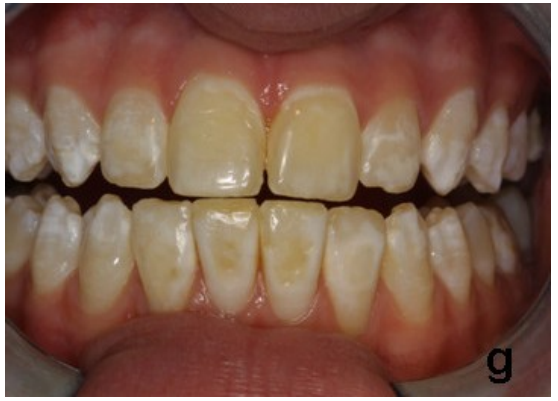


Defects of structure of the teeth

- Genetic disorders

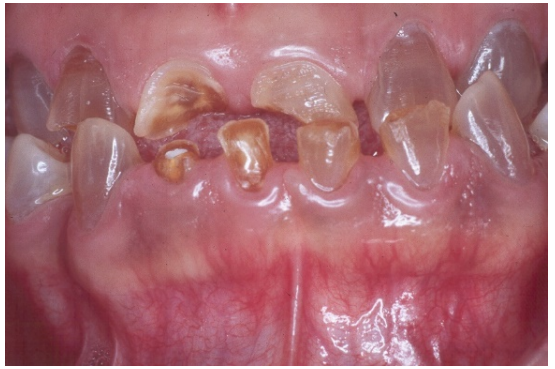
  Amelogenesis imperfecta:

  - changes in the structure (hypoplasia) or mineralization (hypocalcification), presents with abnormal formation of the enamel or external layer of teeth
  - due to the malfunction of the proteins in the enamel
  - People afflicted with amelogenesis imperfecta have teeth with abnormal color: yellow, brown or grey.



  Dentinogenesis imperfecta

  - Genetic disorder of tooth development
  - Inherited in an autosomal dominant pattern
  - Characterised with soft dentine with short roots, discolored (most often a blue-gray or yellow-brown color) and translucent teeth (eg.osteogenesis imperfecta)



- Systemic causes: Measels, Rickets, Hypoparathyroidism, Tetracycline

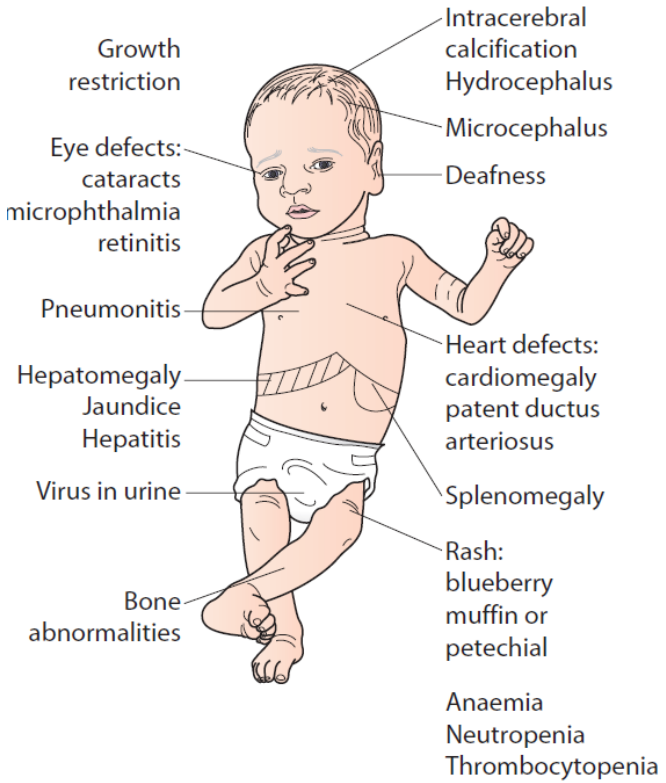
Congenital infections

The original concept of the TORCH perinatal infections was to group five infections with similar presentations, including rash and ocular findings.

These five infections are:

- Toxoplasmosis
- Other (syphilis)
- Rubella
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)

Worldwide incidence of TORCH varies it is up to 10% of congenital infection.



Clinical features of congenital rubella, cytomegalovirus (CMV), toxoplasmosis and syphilis

Congenital rubella

The risk and extent of fetal damage are mainly determined by the gestational age at the onset of maternal infection

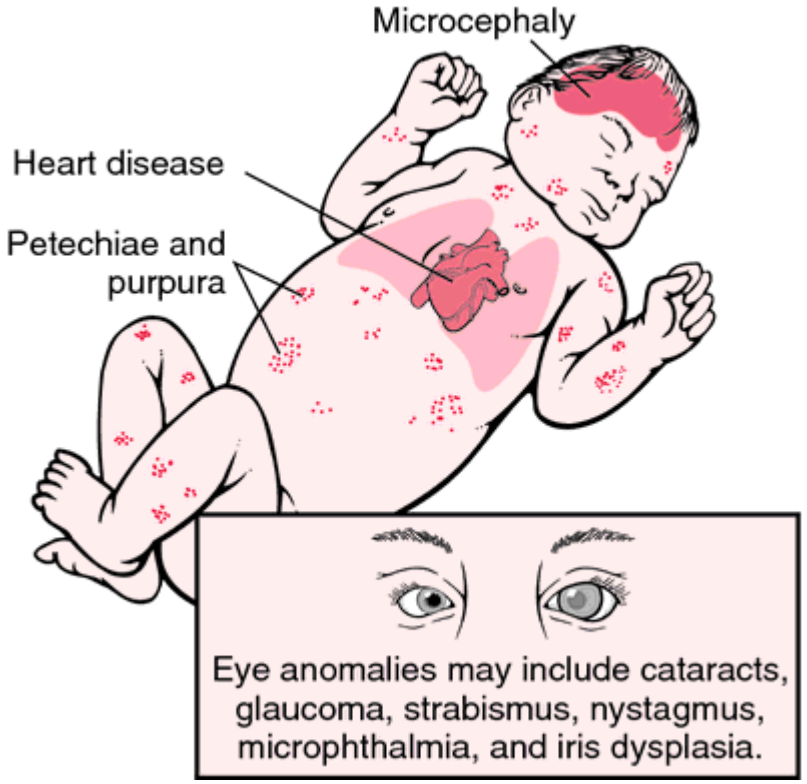
Infection before 8 weeks' gestation causes: deafness, congenital heart disease, cataracts

About 30% of fetuses of mothers infected at 13–16 weeks' gestation have impaired hearing

Beyond 18 weeks' gestation, the risk to the fetus is minimal.

Classic triad:

1. Sensorineural deafness
2. Eye abnormalities - especially retinopathy, cataract, and microphthalmia (43% of patients)
3. Congenital heart disease - especially pulmonary artery stenosis and patent ductus arteriosus



Cytomegalovirus

- CMV is the most common congenital infection
- In Europe, 50% of pregnant women are susceptible to CMV
- About 1% of susceptible women will have a primary infection during pregnancy, and in about 40% of them the infant becomes infected
- The infant may also become infected following an episode of recurrent infection in the mother, but this is much less likely to damage the fetus

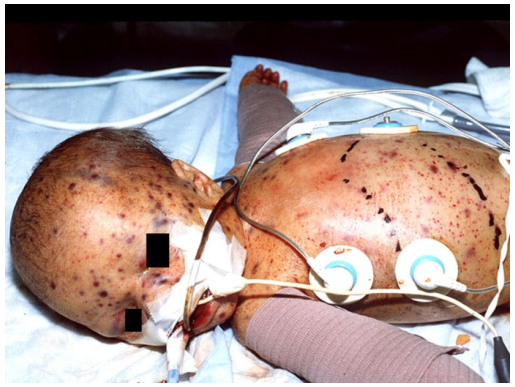
When an infant is infected:

- 90% are normal at birth and develop normally
- 5% have clinical features at birth, such as hepatosplenomegaly and petechiae, neurodevelopmental disabilities such as sensorineural hearing loss, cerebral palsy, epilepsy and cognitive impairment
- 5% develop problems later in life, mainly sensorineural hearing loss.

Clinical manifestation congenital CMV

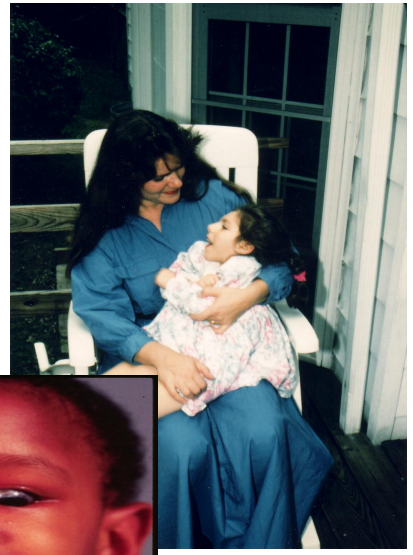
Temporary Symptoms

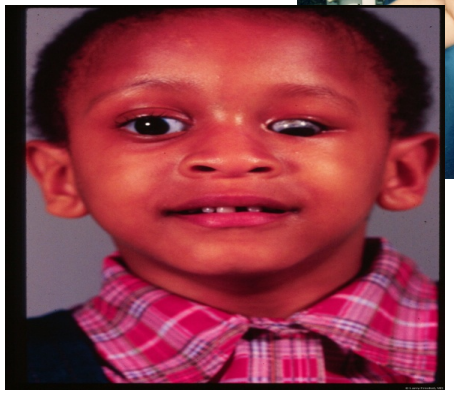
1. Liver failure
2. Hypersplenism
3. Jaundice
4. Petechiae
5. IUGR
6. Seizures



Permanent Symptoms or Disabilities

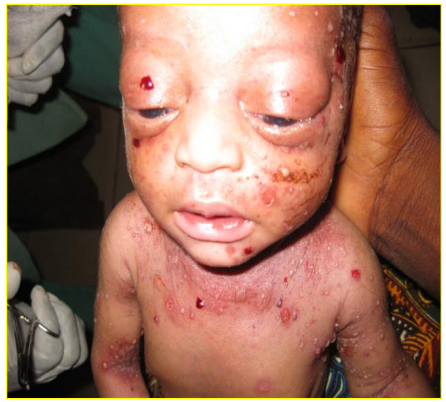
1. Hearing loss
2. Vision loss
3. Mental disability
4. Microcephaly
5. Lack of coordination
6. Seizures

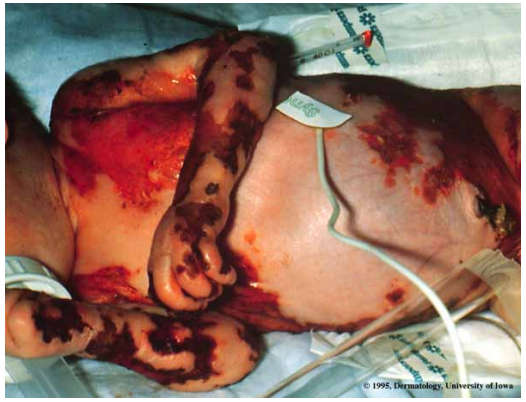




Herpes Simplex Virus

- Usually infection is transmitted close to time of delivery
- Lesions localized on skin, eyes, mouth
- Microcephaly
- Microphthalmos
- Retinal dysplasia
- Hepatosplenomegaly
- Neurological impairment





Varicella (chickenpox)

A total of 15% of pregnant women are susceptible to varicella (chickenpox).

Usually, the fetus is unaffected but will be at risk if the mother develops chickenpox:

1. In the first half of pregnancy (<20 weeks), when there is a <2% risk of the fetus developing severe scarring of the skin and possibly ocular, neurological damage and digital dysplasia
2. Within 5 days before or 2 days after delivery, when the fetus is unprotected by maternal antibodies and the viral dose is high. About 25% develop a vesicular rash. The mortality is 30%.

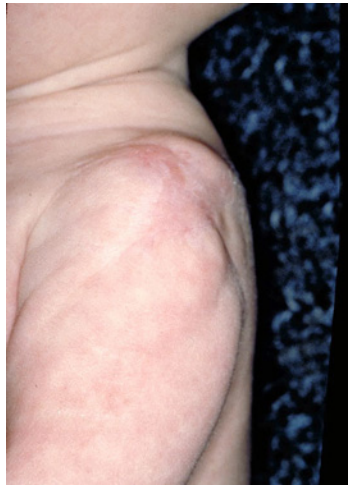
Exposed susceptible mothers can be protected with varicella zoster immune globulin (VZIG) and treated with aciclovir.

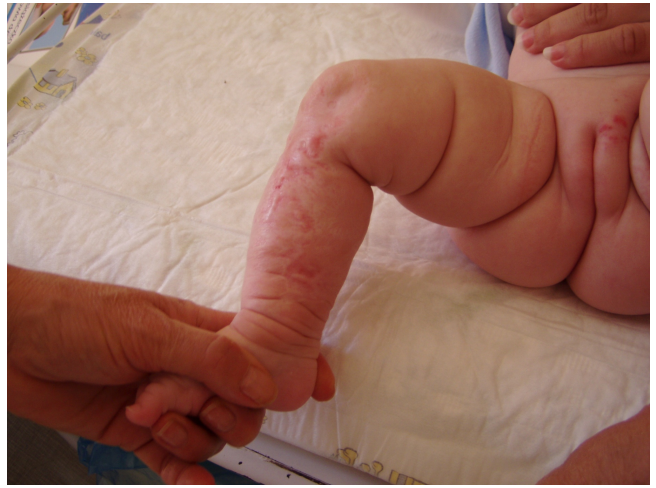
Infants born in the high-risk period should also receive zoster immune globulin and aciclovir prophylactically.

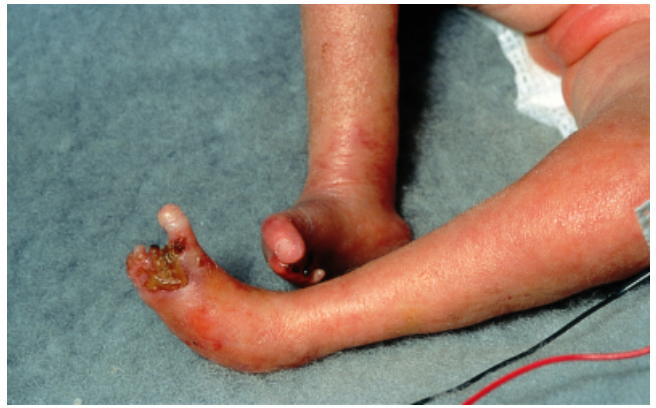
Varicella

Symptoms:

- Limb hypoplasia
- Mental retardation
- Muscle atrophy, scars on the skin
- Microcephaly
- Growth retardation







Toxoplasmosis

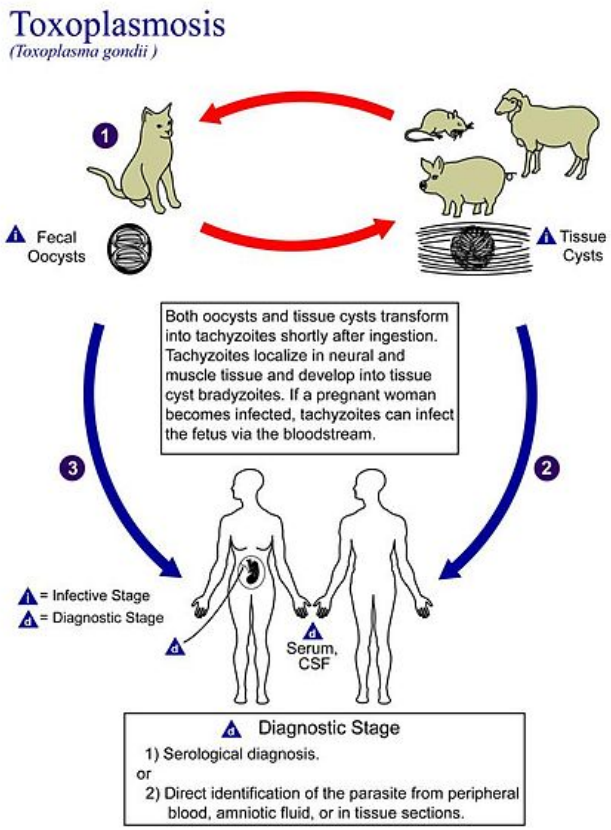
Most infected infants are asymptomatic.

About 10% have clinical manifestations of which the most common are:

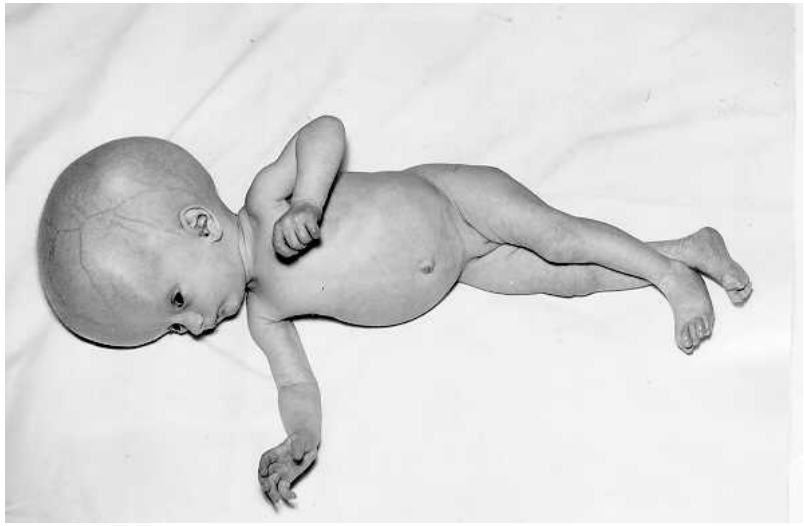
- Retinopathy, an acute fundal chorioretinitis which sometimes interferes with vision
- Cerebral calcification
- Hydrocephalus
- Neurological disabilities

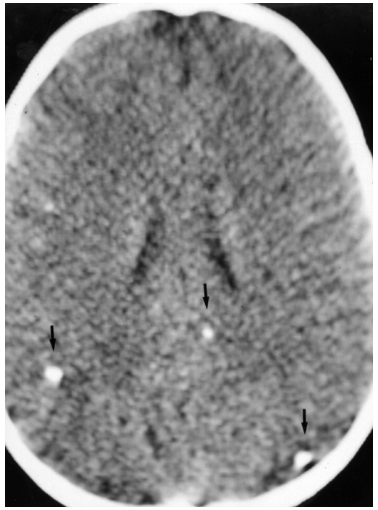
Infected newborn infants are usually treated (pyrimethamine and sulfadiazine) for 1 year.

Asymptomatic infants remain at risk of developing chorioretinitis into adulthood.

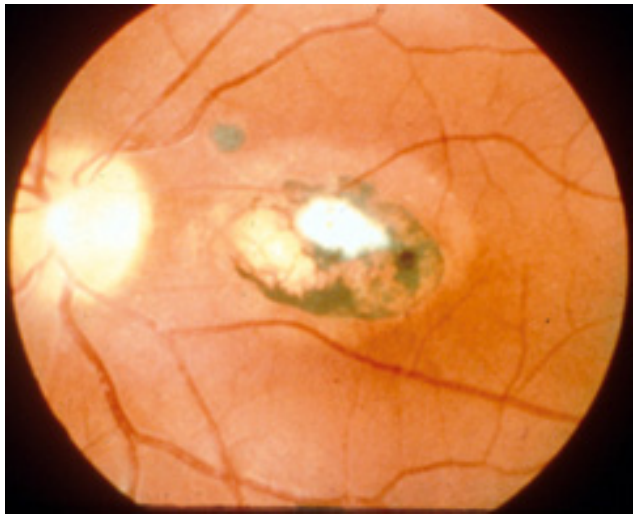


Toxoplasmosis

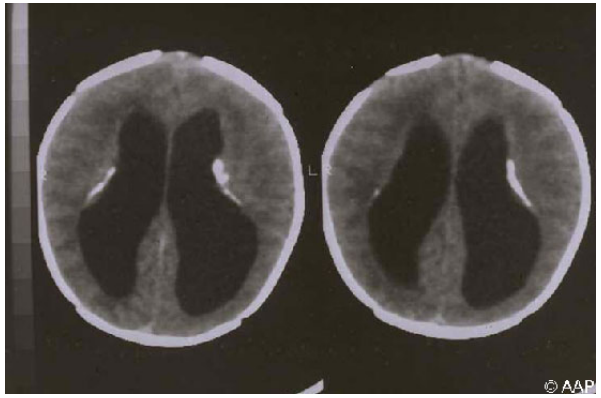




Cerebral calcification



Chorioretinitis



Hydrocephalus

Zika virus

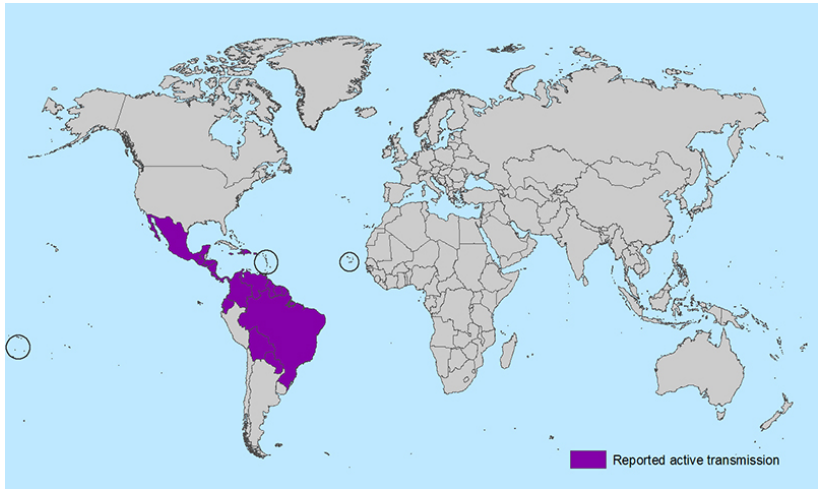
Zika virus disease is caused by a virus transmitted by *Aedes* mosquitoes.

1 in 5 people infected with Zika virus become ill, the most common symptoms of Zika are fever, rash, joint pain, or conjunctivitis .The illness is usually mild with symptoms lasting for several days to a week.

Recently in Brazil, there is observed an increased number of newborns with microcephaly in northeast Brazil.

But… more investigation is needed to better understand the relationship between microcephaly in babies and the Zika virus.

Other potential causes???



Chromosomal & Genetic Factors

- Numerical Abnormalities
  - Trisomy 21 (Down syndrome)
  - Trisomy 18
  - Trisomy 13
  - Klinefelter Syndrome
  - Turner Syndrome
- Structural Abnormalities

Estimated that 50% of all conceptions end in spontaneous abortion and 50% of these have major chromosome abnormalities.

Most common chromosome abnormalities in aborted fetuses is: Turner syndrome (45,X), triploidy, trisomy 16

Down Syndrome

Extra copy of chromosome 21

- Growth retardation
- Varying degrees of mental retardation
- Craniofacial abnormalities
  - Upward slanting eyes
  - Epicanthal folds
  - Flattened facies
  - Small ears
  - Cardiac defects
  - Hypotonia

Most of the time due to meiotic nondisjunction

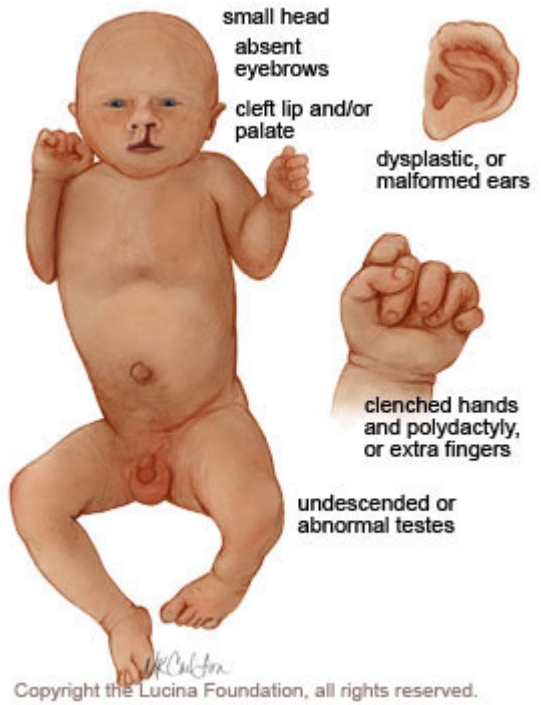
- ⇑ risk in women > 35 (1 in 1000 ⇒ 1 in 400)

Trisomy 18- Edwards syndrome

- Mental retardation
- Congenital heart defects
- Low set ears
- Flexion of fingers & hands
- Micrognathia
- Renal anomalies
- Syndactyly
- Malformations of the skeletal system
- Infants usually die by age 2 months
- Incidence is 1 in 5000

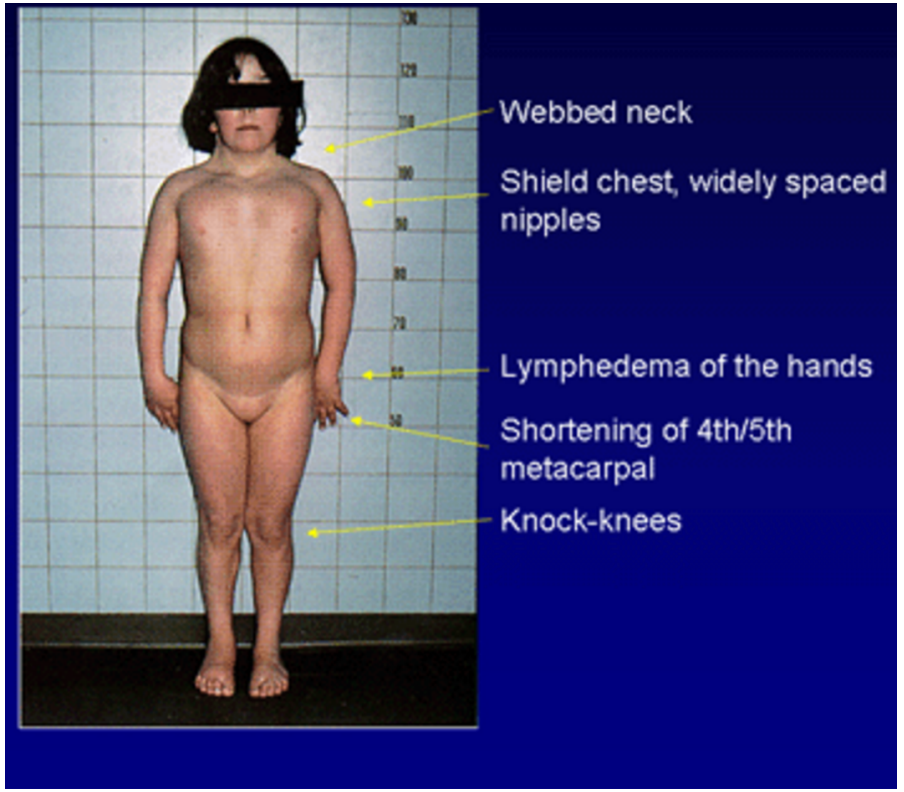
Trisomy 13- Patau syndrome

- Mental retardation
- Holoprosencephaly
- Congenital heart defects
- Deafness
- Cleft lip & palate
- Eye defects
  - Microphthalmia
  - Anophthalmia
  - Coloboma
- Most infants die by age 3 months
- Incidence 1 in 15,000



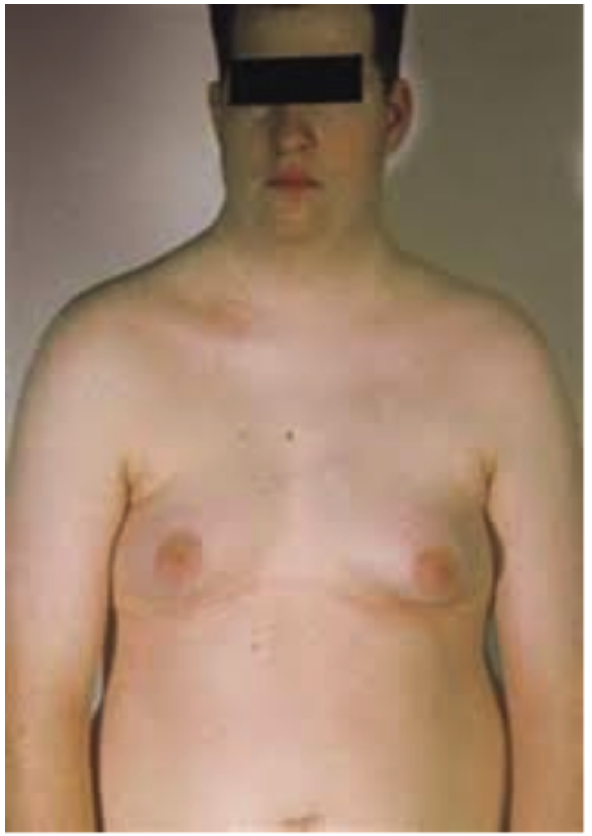
Turner Syndrome

- Absence of ovaries (gonadal dysgenesis)
- Short stature
- Webbed neck (frequently)
- Lymphedema of the extremities
- Skeletal deformities
- Broad chest with widely spaced nipples
- Usually (45, X) missing one X chromosome



Klinefelter Syndrome

- Found only in males (47, XXY most common)
- Usually detected at puberty
- 1 in 500 males
- Nondisjunction of XX homologues
- Sterility
- Testicular atrophy
- Hyalinization of seminiferous tubules
- Gynecomastia
- Mental impairment

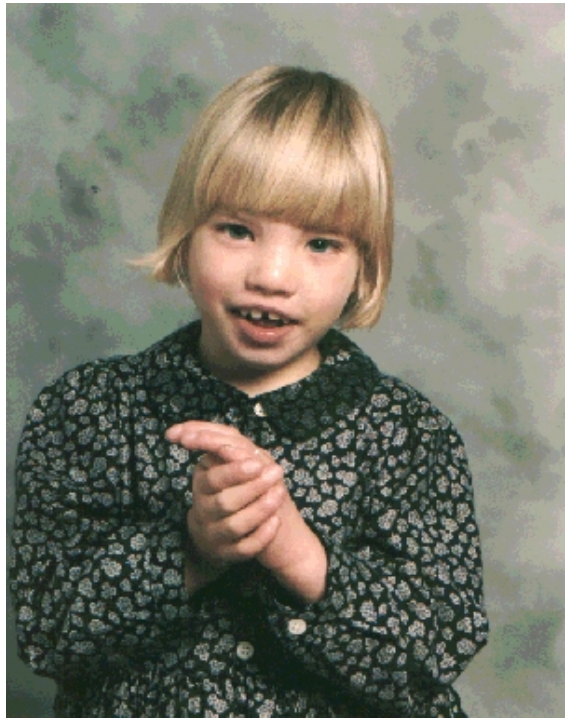


Structural abnormalities

May involve one or more chromosomes

Usually result from chromosome breakage

- Cri-du-chat (cry of the cat) syndrome
  - Partial deletion of chromosome 5
  - Small heads (microcephaly)
  - Unusually round face
  - Small chin
  - HipertelorismV
  - Small nose bridge
  - Heart defects
  - Muscular/skeletal problems
  - Mental retardation



Microdeletion

Microdeletions

- Span a few contiguous genes
- Genomic imprinting
  - Cases that exhibit differential expression depending if the genetic material is from the mother or father
    - Angelman vs. Prader-Willi syndrome

Deletion on long arm of chromosom 15

- Angelman syndrome (maternal chromosome deleted)
  - Mental retardation
  - Cannot speak
  - Exhibit poor motor development
  - Prone to unprovoked & prolonged periods of laughter
- Prader-Willi syndrome (paternal chromosome deleted)
  - Hypotonia
  - Obesity
  - Mental retardation
  - Hypogonadism
  - cryptorchidism

Fragile X sydrome

Fragile sites

- Regions of chromosomes that demonstrate a propensity to separate or break under certain conditions
  - Fragile X syndrome
    - Mental retardation
    - Large ears
    - Prominent jaw
    - Pale blue irides
    - Male (4/2000) vs. females (1/4000)
    - 2ND to Down syndrome as a cause of chromosomally derived mental retardation

Fragile X

Fetal alcohol syndrome

FAS can be defined as congenital disease caused by consumption of alcohol by mother during pregnancy

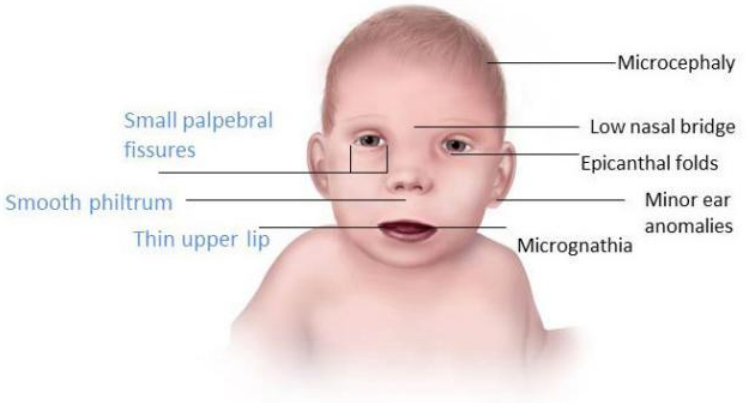
No amount of alcohol consumption is safe during pregnancy.

Symptoms:

- Growth Retardation
- Mental Retardation
- Microcephaly
- Hyperactivity
- Seizures
- Impaired language development
- Facial Features

  Smooth philtrum, Thin upper lip Small eyes , Short upturned nose, Flattened cheeks, Small jaw (maxillae or mandible)

- Heart defect



Refferences and sources

Nelson textbook of Pediatrics, 19th Edition, Kliegman, Behrman, Schor, Stanton, St. Geme

Pediatria, Kawalec, Grenda, PZWL, Warszawa 2013

Illutrated textbook of Pediatrics, 4th Edition

www.who.int

www.congenitalheartdefects.com/stats.html

www.embryology.ch/

genomicdisorders.wikispaces.com/

Google.com

Slideshare.net