

Malformations During Embryonic and Fetal Development

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Congenital malformations are developmental disorders that arise before birth during the embryonic (2nd - 8th week of development) or fetal period (9th - 38th week of development) (from the Latin *congenitus* = "born with"). The cause may be genetic or contingent on external influences. The rate of incidence for children born alive is approximately 3%. Toxic agents that may cause embryonic damage and malformations are called teratogens, and the study of the cause and characteristics of inherent malformations is called teratology (Gr. *teras* = monstrosity, marvel). Infections such as rubella, medications like thalidomide, drugs such as alcohol and tobacco, or radiation are all teratogens.



Note on counting: There are 38 weeks of development post-conception (after fertilization of the egg cell), or 40 weeks of pregnancy (WOPs) post-menstruation (after the last period). You may come across both forms of numbering in exams.

Epidemiology of the Malformations

The incidence rate of malformations is **4-6%** and consists of 2-3% of all newborns and another 2-3% of children up to the age of 5. At around 21%, malformations are the **most**

common cause of child mortality, and are also the **primary cause of disabilities**.

The cause of congenital malformations is only known in 40-60% of cases: 15% of which are due to genetic factors such as chromosomal anomalies and mutations, 10% are due to external causes, 20-25% stem from combinations of genetic and external factors, and 0.5-1% are caused during the development of twins.

Care is necessary with **more minor anomalies**, such as microtia (small ears), pigmented spots or constricted epicanthic folds, as are encountered in 15% of newborns. In 3-20% of cases, they are an indication of a severe malformation, or are part of a syndrome.

Classification of the Malformations

Primary Malformations

Formation during **organogenesis (3rd-8th week of development)** of the embryonic period (2nd-8th week of development), whereby the organ can completely or partially fail, or exhibit structural defects due to genetic or external factors (teratogens). During this time, the embryo is **highly vulnerable to these teratogens** (possible link to section on teratogens later in the text).

Secondary Malformations

Formation via destruction or alteration of already developing organs, such as intestinal atresia due to a vascular change, or defects in the amniotic bands.

Identical (Monozygotic) Twins

These form upon separation of totipotent cells of the zygote during its development into a blastocyst. Two embryos subsequently form with an identical genotype, and these are natural clones.

Fraternal (Dizygotic) Twins

These form upon fertilization of two simultaneously matured egg cells by two spermatozoa. Genetically, they are equivalent to siblings.

Double Malformations



Picture: "Ischiopagus Tripus Conjoined Twins" by Khan YA.
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Two fetuses that have grown together due to incomplete intertwining of the embryoblast in the blastocyst stage on the 13th day after fertilization have a double malformation, and are also called Siamese twins in reference to the famous pair of twins from Siam. Depending on the allocation of organs, which may range from a complete set of organs for each twin to shared organs, post-natal surgical separation is possible.

In the event of a **symmetrical double malformation**, both foetuses have a complete set of organs, whereas with an **asymmetrical malformation**, the uneven allocation leads to allocation to the more developed autosite with the less developed parasite, the development of which can be restricted to a tumour-like attachment in the form of a teratoma at the lowest level.

Terminology of the Malformations

During the embryonic development of the organs, Gr. **organogenesis (3rd - 8th week of development)**, many malformations can arise from many causes. The terms here refer to one organ, but may also refer to different systems in other contexts (e.g. hyperplasia of individual cells in histology).

Agenesis	An organ has not developed.
Aplasia	An organ has developed, but is exhibiting defective differentiation, which may lead to regression or loss of function.
Hypoplasia	An organ only grows insufficiently with an unchanging cell count (e.g. due to nutrient deficiency), which often leads to functional disabilities.
Hyperplasia	An organ has grown too large with an unchanging cell count (e.g. due to increased functional requirements), which often leads to functional disabilities.
Dysplasia	Abnormal cell differentiation leads to altered tissue of the organ affected.
Dystopia	An organ is not located in its normal physiological location.
Heterotopia	Typically differentiated tissue is found dispersed in one or more non-typical locations in the body. When embryonic tissue is found in a non-typical location, this is called choristia .
Deformations	Formation by mechanical forces usually affects the locomotor system. For instance, clubfoot can result from the amniotic cavity being too narrow.

Dysraphism (from Gr. <i>raphe</i>: seam)	Defective end of the neural tube, which can affect various organ systems. One well-known example of a defective neural tube end near the spine is spina bifida (possible internal link).
Stenosis	Constriction within a (hollow) organ.
Atresia	Absence of the physiological opening or the lumen of a (hollow) organ, or occlusion thereof.
Syndromes	Include multiple malformations with the same cause and in a characteristic combination, e.g. resulting from trisomy 21 – Down's syndrome.
Persistence	Continued existence of an organ or part of an organ that, physiologically, only exists for a limited period during embryonic development.
Association	Describes the frequent appearance of two or more malformations with an unknown shared cause.

Teratogenicity

Multiple factors determine whether a fetus will develop a malformation. The following **principles of teratology** were first formulated by James G. Wilson in 1959.

Whether or not a malformation will arise, initially depends on the genetic constitution of the fetus, the maternal genome with regard to vulnerability to toxins, and the stage of development.

The stage of development most vulnerable to the influence of teratogens is the **organogenesis of the 3rd-8th week of development** during the embryonic period.

Of course, the effects of the teratogen depend on the **dosage and duration of exposure**, as well as the specific mechanism of action.

The **characteristics** of the developmental disorder have varying degrees of severity: embryonic death, malformations, growth retardation or functional disabilities, such as neurological or physical disorders, may occur.

Malformations: The Role of Exogenous Factors (Teratogens)

Teratogens, or substances that may harm the embryo, are manifold.

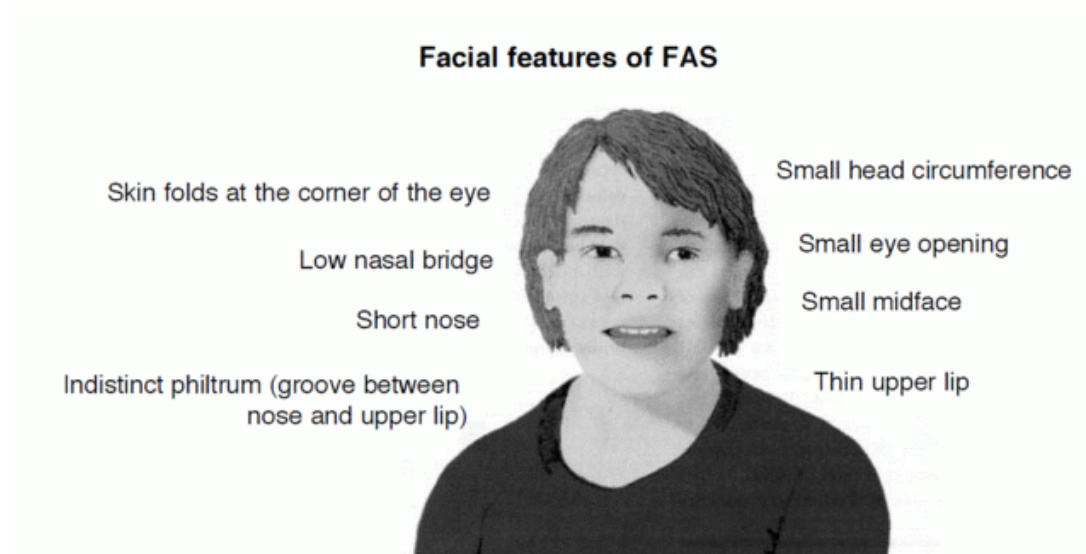
Infections

Severe embryopathies, such as vision disorders, heart disorders and mental impairment due to neural damage, may be caused by viruses (**rubella**, CMV (**cytomegalovirus**), HSV (**herpes simplex virus**), chicken pox (**varicella virus**), AIDS (**HI virus**)), bacteria (syphilis from **treponema pallidum**) and protozoa (toxoplasmosis from **toxoplasma gondii**).

Physical Impairment

Radiation, X-rays or hyperthermia (UV rays) can lead to micro-/anencephaly, cleft palate and mental impairment.

Chemical Factors



These include drugs and medications. **Smoking** during pregnancy can lead to growth delays with a lower birth weight, which, in turn, increases mortality among infants. In the worst case scenario, **alcohol abuse** can result in fetal alcohol syndrome, with mental impairment and typical facial anomalies.



Picture: "Photograph of right forearm affected by birth defect Amelia" by Onearmedbandit86.
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Examples of **medications** that penetrate the placental barrier are thalidomide (resulting in malformations of the extremities, e.g. amelia/meromelia, and heart disorders), anticonvulsives such as phenytoin or valproic acid (resulting in organ malformations and mental impairment), and antibiotics such as tetracycline (resulting in dental diseases or deafness). Any ingestion of medication during pregnancy should be assessed as closely as possible for possible contra-indications!

Hormones

Ingested steroid hormones may lead to the masculinisation of female genitals; estrogen to malformations of female and male sex organs.

Diseases of the Mother

These may also entail risks. For instance, maternal diabetes may lead to heart disorders, neural tube defects and other malformations. (Generally worsening) maternal obesity (adipositas) may cause heart malformations or omphaloceles.

Paternal Causes

These stem from impairments in the paternal genotype that may be caused by advanced age, exposure to environmental toxins, alcohol and cigarette smoke.

Phase Dependency of the Malformations

Depending on the current phase of development of the embryo or fetus, its vulnerability to impairments, which can have very different manifestations, varies.

In the event of a **gametopathy**, there exists a pre-conception impairment of the maternal or paternal gamete. This results in structural or numerical chromosome defects that usually lead to the death of the gamete and (unnoticed) abortion.

Blastopathy describes impairments of the fertilized blastocyst (1st-14th day post-conception), resulting in it fruitlessly settling into and dying in the uterus by the all-or-nothing principle. The possible development of double malformations and identical twins must be emphasized during this phase.

All impairments of the organs during organogenesis (2nd-8th week of development) are referred to as an **embryopathy**. During this time, the developing organs are **especially vulnerable to teratogens** depending on the peak of mitosis. The result may be malformations of the entire embryo, individual organs or the placenta.

During the fetal period (9th-38th week of development) the organs continue to mature and differentiate. **Foetopathies** from this period can lead to functional disabilities, as the brain is especially vulnerable to teratogens.

Organ Development: Phase-Dependent Vulnerability for Malformations

During organogenesis (3rd-8th week of development), the embryo is particularly vulnerable to teratogens. In this overview, the organs are listed by their temporal sequence of development with possibilities for impairment.

CNS, neural tube (3rd-32nd - 40th week of development): the CNS grows from the neural tube, which protrudes from the neurectoderm. Impairment may result in neural tube defects, such as spina bifida and mental disability.

Heart (3rd-7th - 9th week of development): the heart grows from the lateral plate mesoderm. About every 100th newborn comes into the world with a heart defect. The most common are truncus arteriosus communis, atrial septal defect (ASD) and ventricular septum defect (VSD). These may also be indications of a syndrome.

Extremities (4th-6th - 9th week of development): the extremities are mesenchymal in origin, and also stem from the lateral plate mesoderm. The symptoms of meromelia (Gr. *melia* - extremity)/amelia, or the lack of parts or all of one or more extremities, are due to impairments during this time. One well-known cause was the ingestion of thalidomide (Contergan®), sold as sleep medicine in the 1960s.

Ears (4th-10th - 32nd week of development): if the ear, developing from the ectodermal inner ear and tuba auditiva, as well as the tympanus from the endoderm, is damaged during this vulnerable time, the result may be deafness, auricular dysplasia or a

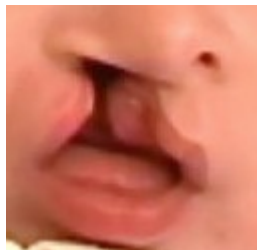
deep base of the ear.

Respiratory tract (4th-16th - 40th week of development): the respiratory tract combines with the mucosa of the mouth and nose from the surface ectoderm, and the respiratory epithelium from the endoderm. Impairments here may result in fistulas, stenoses and atresia, or fetal acute respiratory distress syndrome (ARDS) in the case of a lack of surfactant formation.

Urogenital system (4th-16th - 40th week of development): the shared mesodermal precursor is the pronephric duct, from which the kidneys and the deviating urinary passages, and the sex organs (via the Wolffian and Müllerian ducts), form. One common malformation is the urachal fistula after persistent connection of the urinary bladder with the navel, upon which urine is discharged by the navel of the infant upon activation of the abdominal press.

The various movements of the organs involved during embryogenesis must also be considered: For instance, the kidney ascends while the testicles descend.

Gastrointestinal tract (GIT; 5th-32nd - 40th week of development): the mucosa of the gastrointestinal tract is allocated to the endoderm, and the stomatodaeum and anal region to the ectoderm; the glands flowing into them, including the liver, gallbladder and pancreas, originate in the endoderm. Along with stenoses and atresia of all systems involved, impairments may also result in rotational disabilities (see twisted stomach) or lead to umbilical hernias as the result of temporary, extra-foetal localization of the intestine, such as in the form of an omphalocele.



Picture: "Vollständige Lippen-Kiefer-Gaumenspalte rechts" by Trelawney. Licence: [CC BY-SA 3.0](#)

Face, lips, palate (5th/6th-7th/8th - 16th week of development): the face develops from five mesenchymal facial processes, which form from neural crest cells. Should the epithelia be unable to fully make contact, or if there is a lack of proliferation or a break-up of already forming coalescence zones, such as the medial nasal prominence and the maxillary process, the relatively common cleft lip and palate may develop (or partial manifestations: cleft lip, cleft palate) with an incidence rate of approximately 1:1000.

Clinical Reference: Prevention

Multiple preventative strategies can greatly decrease the occurrence of malformations. They should primarily be applied before conception.

- Inoculation of the mother against rubella
- Folic acid substitution during pregnancy lowers the incidence of neural tube

defects

- Iodation of drinking water and table salt prevents developmental impairments of the thyroid (cretinism)
- Abstinence from alcohol and cigarettes
- Good assortment of medication for metabolic diseases of the mother
- As a doctor, consider teratogenicity when prescribing medication for women of child-bearing age

Review Questions

The solutions can be found beneath the bibliography.

1. During an abdominal press on a child, fluid is discharged from the navel. What is the most likely cause for this discharge?

- A. Innate umbilical hernia
- B. Defective regression of the ligamentum umbilicale mediale
- C. Non-obliterated plica umbilicalis lateralis
- D. Urachal fistula
- E. Aberrant ureter

2. (Lateral) cleft lip and cleft palate are most likely to form from defects upon coalescence of the

- A. Medial nasal prominence and maxillary process
- B. Lateral nasal prominence and maxillary process
- C. Frontal convolution and maxillary process
- D. Right and left palatal plate
- E. Lateral and medial nasal prominence

3. For which of these organs can inherent malformations be ascribed to defects of the neural crest/neural crest cells the earliest?

- A. Heart
- B. Testicles
- C. Lungs
- D. Spleen
- E. Kidney

4. Which of these statements about Siamese twins is the most likely?

- A. They develop when two oocytes form in an ovarian follicle.
- B. They can have shared internal organs (e.g. the heart).
- C. They usually share an umbilical cord.
- D. They are usually linked at the extremities.
- E. They are often of different genders.

References

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Correct answers: 1D, 2A, 3A, 4B

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Notes