Twinning and Teratology

1. Twinning:
   ✓ dizygotic twins
   ✓ monozygotic twins

2. Teratology – history and principles

3. Teratogens:
   ✓ environmental factors
   ✓ chromosomal and genetic factors

4. Congenital malformations:
   ✓ functional defects & minor anomalies
   ✓ major structural anomalies (birth defects)
Multiparity in humans

- **uniparity** – the normal condition in humans

- **multiparity incidence (multiple birth):**
  - twins - 1:80 of singleton births
  - triplets - 1:80² = 1:6400
  - quadruplets - 1:80³ etc.

- **multiple pregnancy:**
  - ovarian stimulation with gonadotropins
    - *in vitro* fertilization
    - artificial insemination
  - twins:
    - 125 million ~1.9% of the world population
    - premature birth – ~37 weeks pregnancy
    - lower birth weight, higher mortality risk
  - Yoruba – a large Nigerian ethnic group:
    - the highest rate of twinning in the world
    - 45 twins per 1000 live births (4.5%)
    - high consumption of a specific type of yam
      - natural hormone phytoestrogen

*Prof. Dr. Nikolai Lazarov*
Twinning

- twinning – the bearing of two children at one birth
- twins – offspring produced in the same pregnancy and born during the same birth
  - **monozygotic (identical) twins**
    - multiple (typically two) fetuses produced by the splitting of a single zygote
  - **dizygotic (fraternal) twins**
    - multiple (typically two) fetuses produced by two zygotes
  - **polyzygotic twins**
    - multiple fetuses produced by two or more zygotes
  - **conjoined (Siamese) twins**
Dizygotic twins

- **fraternal (biovular) twins:**
  - ⅔ (~70%) of all twin pregnancies
  - 7-11/1000 births
  - increased incidence
    - with maternal age
    - after assisted reproduction

- **special features:**
  - simultaneous shedding of two oocytes ⇒ two zygotes, implanted individually in the uterus
  - independently fertilized by two different spermatozoa
  - each embryo has its own amnion, chorion and placenta ⇒ dichorionic/diamnionic fetus
  - fusion of the two placentas ⇒ erythrocyte mosaicism
  - may or may not be of different sex
  - different external features
  - different constitution:
    - genetic – share the same chromosome profile
    - immunologic
    - blood groups

Prof. Dr. Nikolai Lazarov
Monozygotic twins

- identical (uniovular) twins:
  - ⅓ of twins – ~30% of all twins
  - 3–4/1000 live births
  - total number – 10 million (2006)
  - 0.2% of the world population

- special features:
  - develop from a single fertilized ovum ⇒ one zygote
  - fertilized by a single spermatozoon
  - result of splitting of the zygote at various stages of development ⇒
    - two blastomeres:
      - separate placentas, amnion and chorion (dichorionic/diamnionic)
      - monochorionic/diamnionic
      - monochorionic/monoamnionic
  - conjoined (Siamese) twins
  - always the same sex
  - identical external appearance
  - identical constitution:
    - genetic
    - immunologic
    - blood group

Prof. Dr. Nikolai Lazarov
Teratology

- teratology (Gr. τέρας, τέρατος, monster):
  - the study of perceived abnormalities in the natural world, both real and imagined
  - Etienne Geoffray Saint-Hillar (1772-1844)

- History of teratology:
  - ancient times, the middle ages, Renaissance
  - the scientific era – experimental teratology
    - Mary Shelley’s Frankenstein (1818)

- Principles of teratology:
  - susceptibility to teratogenesis depends on the genotype of the conceptus and maternal genome
  - susceptibility to teratogens varies with the developmental stage at the time of exposure
  - manifestations of abnormal development depend on dose and duration of exposure to a teratogen
  - teratogens act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis
  - manifestations of abnormal development are death, malformation, growth retardation, and functional disorders
Teratogenesis

- teratogenesis (monster making):
  - the formation of a fetal monstrosity
  - production of congenital malformations

- teratogenic causes:
  - unknown – 40-60%
  - genetic factors – 15-18%
    - chromosome abnormalities
    - mutant genes
  - environmental factors – 7-10%
  - multifactorial inheritance – 20-25%
    - a combination of genetic and environmental influences
  - twinning causes – 0.5-1%
Teratogenic agents

- Teratogens – factors that
  - cause anomalies

- teratogenic factors:
  - environmental factors
  - genetic factors
  - chemical agents

- effects of teratogens:
  - maternal & fetal genotype
  - dose and duration of exposure to the agent
  - stage of development

- phases:
  - ‘sensitive’ – blastogenesis and embryogenesis
  - ‘critical’ – periods:
    - preembryonic
    - embryonic
    - fetal

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Congenital Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious agents</td>
<td>Cataracts, glaucoma, heart defects, deafness, teeth</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>Microcephaly, blindness, mental retardation, fetal death</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Microphthalmia, microcephaly, retinal dysplasia</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Limb hypoplasia, mental retardation, muscle atrophy</td>
</tr>
<tr>
<td>Varicella virus</td>
<td>Microcephaly, growth retardation</td>
</tr>
<tr>
<td>HIV</td>
<td>Hydrocephalus, cerebral calcifications, microphthalmia</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Mental retardation, deafness</td>
</tr>
<tr>
<td>Syphilis</td>
<td></td>
</tr>
<tr>
<td>Physical agents</td>
<td>Microcephaly, spina bifida, cleft palate, limb defects</td>
</tr>
<tr>
<td>X-rays</td>
<td>Anencephaly, spina bifida, mental retardation, facial defects</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Chemical agents</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Limb defects, heart malformations</td>
</tr>
<tr>
<td>Aminopterin</td>
<td>Anencephaly, hydrocephaly, cleft lip and palate</td>
</tr>
<tr>
<td>Diphenhydantoin (phenytoin)</td>
<td>Fetal hydantoin syndrome: facial defects, mental retardation</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Neural tube defects, heart, craniofacial, and limb anomalies</td>
</tr>
<tr>
<td>Trimethadione</td>
<td>Cleft palate, heart defects, urogenital and skeletal</td>
</tr>
<tr>
<td></td>
<td>abnormalities</td>
</tr>
<tr>
<td>Lithium</td>
<td>Heart malformations</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Cleft lip and palate, heart defects</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Chondrodysplasia, microcephaly</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Growth retardation, fetal death</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Growth retardation, microcephaly, behavioral</td>
</tr>
<tr>
<td></td>
<td>abnormalities, gastrochisis</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Fetal alcohol syndrome, short palpebral fissures,</td>
</tr>
<tr>
<td></td>
<td>maxillary hypoplasia, heart defects, mental retardation</td>
</tr>
<tr>
<td>Isotretinoin (vitamin A)</td>
<td>Vitamin A embryopathy: small, abnormally shaped ears,</td>
</tr>
<tr>
<td>Industrial solvents</td>
<td>mandibular hypoplasia, cleft palate, heart defects</td>
</tr>
<tr>
<td>Organic mercury</td>
<td>Low birth weight, craniofacial and neural tube defects</td>
</tr>
<tr>
<td>Lead</td>
<td>Neurological symptoms similar to those of cerebral palsy</td>
</tr>
<tr>
<td>Hormones</td>
<td>Growth retardation, neurological disorders</td>
</tr>
<tr>
<td>Androgenic agents</td>
<td>Masculinization of female genitalia: fused labia, clitoral</td>
</tr>
<tr>
<td>(ethisterone, nor ethisterone)</td>
<td>hypertrophy</td>
</tr>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>Malformation of the uterus, uterine tubes, and upper</td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>vagina; vaginal cancer; malformed tests</td>
</tr>
<tr>
<td></td>
<td>Variety of malformations; heart and neural tube defects</td>
</tr>
<tr>
<td></td>
<td>most common</td>
</tr>
</tbody>
</table>
Environmental factors

- **Environmental factors:**
  - infectious agents:
    - rubella virus or German measles
    - cytomegalovirus
    - herpes simplex, varicella and human immunodeficiency (HIV) viruses
    - other viral infections and hyperthermia
    - toxoplasmosis and syphilis
  - maternal diseases:
    - diabetes
    - phenylketonuria
  - radiation – ionizing radiation
  - heavy metals – organic Hg, Pb
  - hypoxia
  - nutritional deficiencies
  - obesity – BMI >29kg/m²
  - alcohol consumption
  - drugs and joint
  - cigarette smoking
  - hormones
Genetic factors

- Genetic factors:
  - chromosomal abnormalities
  - gene mutations

- chromosomal abnormalities:
  - structural – chromosome breakage:
    - translocations
    - deletions - cri-du-chat syndrome
    - ring chromosomes
    - duplications
    - inversions
  - numerical – aneuploidy:
    - monosomy
    - trisomy 13 (Patau syndrome)
    - trisomy 18 (Edwards syndrome)
    - trisomy 21 (Down syndrome)
  - sex chromosome abnormalities:
    - Kleinfelter syndrome – 47, XXY
    - Turner syndrome – 45, X0

- gene mutations – single gene mutations
Chemical agents

- Thalidomide ⇒ phocomelia
  - babies born with limbs that look like flippers on a seal

- Thalidomide:
  - released into the market in 1957 in West Germany
  - primarily prescribed as a sedative or hypnotic to cure "anxiety, insomnia, gastritis, and tension"
  - infants born with the qualities of phocomelia

Prof. Dr. Nikolai Lazarov
Types of anomalies

- congenital malformations (anomalies, birth defects):
  - structural, behavioral, functional and metabolic disorders present at birth
- malformations – during organogenesis (3rd – 8th week of gestation):
  - complete or partial absence of a structure
  - alterations in its normal configuration
- disruptions – due to destructive processes:
  - morphological alterations of already formed structures
- deformations – due to mechanical forces:
  - often involve the musculoskeletal system
  - may be reversible postnatally
- syndrome:
  - group of anomalies occurring together that have a specific common cause
- association:
  - nonrandom appearance of two or more anomalies that occur together more frequently than by chance alone
Congenital malformations

- minor morphological abnormalities – 15% of newborns:
  - microtia (small ears), pigmented spots etc.
  - frequently associated with major defects
- major structural anomalies (birth defects) – 4-6%:
  - 2-3% of liveborn infants
  - 2-3% in children by age 5 years
  - leading cause for ~21% of all infant deaths
Congenital malformations

- **important birth defects:**
  - neural tube defects (one in 1000 live births) – either stillborn or die shortly after birth
    - spina bifida, anencephaly, meningocele etc.
  - defects of other organs:
    - locomotor apparatus and cardiovascular system
    - digestive and respiratory system
    - urogenital system
Limb malformations

- **limb abnormalities:**
  - amelia
  - hemimelia
  - meromelia
  - phocomelia etc.

- **digital anomalies:**
  - ectrodactyly
  - polydactyly
  - syndactyly
  - brachydactyly

- bird-boy

**TABLE 10-2 Common Structural Types of Limb Malformations**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amelia (ectromelia)</td>
<td>Absence of an entire limb</td>
</tr>
<tr>
<td>Acheiria, apodia</td>
<td>Absence of hands, feet</td>
</tr>
<tr>
<td>Phocomelia</td>
<td>Absence or shortening of proximal limb segments</td>
</tr>
<tr>
<td>Hemimelia</td>
<td>Absence of pre- or postaxial parts of limb</td>
</tr>
<tr>
<td>Meromelia</td>
<td>General term for absence of part of a limb</td>
</tr>
<tr>
<td>Ectrodactyly</td>
<td>Absence of any number of digits</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Excessive number of digits</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>Presence of interdigital webbing</td>
</tr>
<tr>
<td>Brachydactyly</td>
<td>Shortened digits</td>
</tr>
<tr>
<td>Split hand or foot</td>
<td>Absence of central components of hand or foot</td>
</tr>
</tbody>
</table>

*Prof. Dr. Nikolai Lazarov*
Twin defects

- asymmetrically conjoined twins:
  - parasitic twins
  - incidence – 10% of cases

- types:
  - autosite
    - the independent twin of a pair of conjoined twins
    - normal, fairly well developed
  - parasite
    - smaller and less formed, severely underdeveloped
Conjoined twins

- conjoined (Siamese) twins:
  - identical twins whose bodies are joined *in utero*
  - incidence – 1:50000-100000 births
  - overall survival rate is approximately 25%
  - more frequently (3:1) found among females

- types of conjoined twins:
  - craniopagus (6% of cases)
  - thoracopagus (56%)
  - pygopagus – less common
Separation of conjoined twins

And on a happier note... Siamese twins who were separated at birth were rejoined today after twenty-three years!

"Well so much for the second opinion, should we try for two more?"

Thank you...