

Teratology

Wendy Chung, MD PhD

Mrs. B

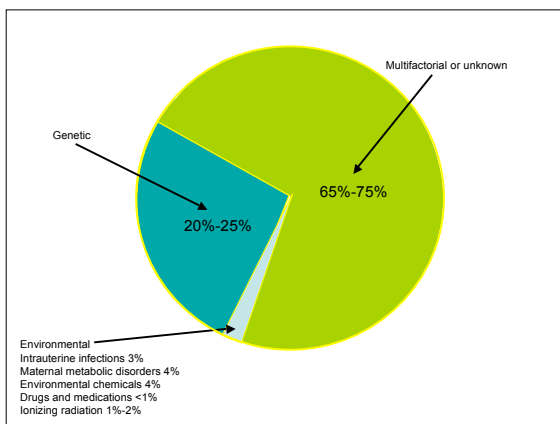
- 30 year old woman comes to you because her 20 week prenatal ultrasound showed a hole in the heart
- Patient and her husband have many questions:
 - What caused this birth defect?
 - Was it caused by the glass of wine she had before she found out she was pregnant?
 - Will there be other problems for this child?
 - If they have other children, what is the risk of recurrence?

Teratology

- The study of abnormal development in embryos and the causes of congenital malformations or birth defects

Birth Defects

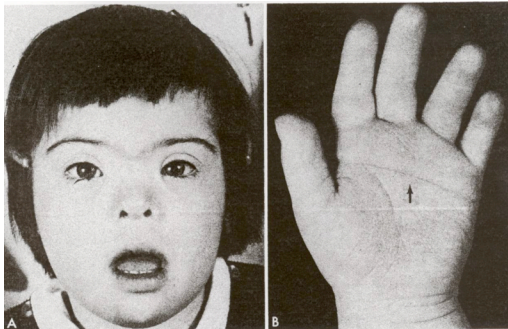
- Observed in 3% of newborns
- Observed in another 3% of children later
- May or may not be outwardly visible
- Etiology: genetic and environmental



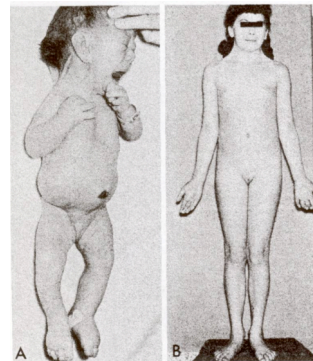
Major and Minor Anomalies

- Major anomalies: life/health threatening
- Minor anomalies: cosmetic
- The greater the number of minor anomalies, the greater the likelihood of a major anomaly
- Certain minor anomalies suggest specific major anomalies

Down Syndrome



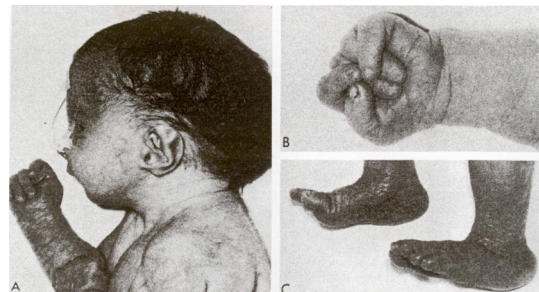
Turner Syndrome



Trisomy 13

- Midline defects (cleft lip and cleft palate)
- Central nervous system malformations
- Micro-ophthalmia
- Congenital heart disease
- Poor growth

Trisomy 18



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- Extensive ultrasound examination does not identify other major anomalies
- Can minor anomalies be excluded?
- An amniocentesis is performed and is normal
- Are genetic etiologies excluded?

Inborn Errors of Metabolism Causing Birth Defects

- Smith Lemli Opitz
- Congenital disorders of glycosylation
- Fatty acid oxidation disorders

Single genes cause developmental disorders

- PAX6: aniridia
- NEUROD1: pancreatic agenesis
- TTF1: thyroid agenesis
- NKX2.5: congenital heart disease
- ZIC3: holoprosencephaly
- Doublecortin: lissencephaly

Achondroplasia



Teratogens

- A chemical, infectious agent, physical condition, or deficiency that, on fetal exposure, can alter fetal morphology or subsequent function
- Teratogenicity depends upon the ability of the agent to cross the placenta
- The embryo is most susceptible to teratogenic agents during periods of rapid differentiation

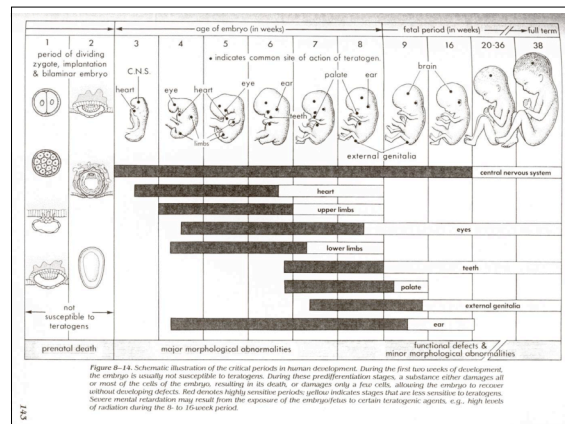


Figure 8-14. Schematic illustration of the critical periods in human development. During the first two weeks of development, the embryo is usually not susceptible to teratogens. During these pre-differentiation stages, a substance either damages all or most of the cells of the embryo, resulting in its death, or damages only a few cells, allowing the embryo to recover without developing defects. First denotes highly sensitive periods; germline indicates stages that are less sensitive to teratogens. Severe mental retardation may result from the exposure of the embryo/fetus to certain teratogenic agents, e.g., high levels of radiation during the 6- to 16-week period.

Tissue	Malformation	Defect	Timing of Cause	Additional Information
Cerebral system	Hidrocerephaly	Prechordal mesoderm	23 days	Associated facial defect
	Anencephaly	Closure of anterior neural tube	26 days	Subsequent development of forebrain
Face	Meningocele	Closure in portion of posterior neural tube	28 days	80% lumbosacral
	Cleft lip	Closure of lip	36 days	42% associated with cleft palate
	Branchial sinus or cyst	Regression of branchial cleft	8 weeks	Preauricular and other sites attached to dermo-ectoderm
Neck	Rubin sequence	Early mandibular hypodermis	9 weeks	Li-shaped posterior limb plate
	Cleft maxillary palate	Fusion of maxillary palatal shelves	10 weeks	
Abdomen	Esophageal atresia and tracheoesophageal fistula	Lateral separation of foregut into trachea and foregut	30 days	
	Posterior neural crest migration	Lymphaticovenous communication	40 days	Common in VZV, Turner's syndrome
	Rectal atresia with fistula	Lateral separation of distal foregut	6 weeks	
Diaphragm	Septum	and septal arch	8 weeks	
	Diaphragmatic hernia	Closure of diaphragmatic canal	7-8 weeks	
	Duodenal atresia	Recanalization of duodenum	10 weeks	Associated incomplete or absent mesenteric attachments
Omphalocele	Malrotation of gut	Rotation of intestinal loop to the stomach	10 weeks	
	Malrotation of gut	Return of midgut from yolk sac to abdomen	10 weeks	
Circulatory system	Meckel diverticulum	Obstruction of septum	10 weeks	May contain gastric or pancreatic tissue
	Exposition of bladder	Migration of mesonephros	30 days	Associated meckel's diverticulum and other genital defects
Hypoplasia	Laryngeal obstruction syndrome	Usually genetic; urethra valves	9 weeks	More common in males
	Bicuspid aortic valve	Fusion of lower portion of aortic arch	10 weeks	
Heart	Hypoplasia	Fusion of ventral folds (dorsal aorta)	12 weeks	
	Cryptorchidism	Descent of testis into scrotum	7-9 months	
Vertebral column	In-transposition of great vessels	Directional development of foregut	14 days	
	Vertebral arch defect	Closure of vertebral arch	6 weeks	
Limb	Phenylketonuria	Closure of ducts	6-10 months	
	Agenesis of radius	Atresia of radial bone	10 days	Often accompanied by other defects of limb; risk of distal
Severe conductive	Separation of digital rays	6 weeks		

How are agents determined to be teratogenic ?

- Anecdotal data in humans
- Data from animal studies

Effect of Exposure Depends on Timing

- All or none effect early
- Effect of organogenesis during embryonic development
- Effect on size and function during fetal development

Teratogens	Congenital Malformations
Androgenic Agents Ethinisterone Norethinisterone Testosterone	Varying degrees of masculinization of female fetuses: ambiguous external genitalia caused by labial fusion and clitoral hypertrophy.
Drugs and Chemicals Alcohol	<i>Fetal alcohol syndrome</i> : intrauterine growth retardation (IUGR); mental retardation; microcephaly; ocular anomalies; joint abnormalities; short palpebral fissures.
Aminopterin	Wide range of skeletal defects; IUGR; malformations of the central nervous system, notably microencephaly (a large part of the brain is absent).
Busulfan	Stunted growth; skeletal abnormalities; corneal opacities; cleft palate; hypoplasia of various organs.
Phenytoin (Dilantin)	<i>Fetal hydantoin syndrome</i> : IUGR; microcephaly; mental retardation; ridged metopic suture; inner epicanthal folds; eyelid ptosis; broad depressed nasal bridge; pharyngeal hypoplasia.
Lithium carbonate	Various malformations, usually involving the heart and great vessels.
Methotrexate	Multiple malformations, especially skeletal, involving the face, skull, limbs, and vertebral column.
Large doses of retinoic acid (Vitamin A)	Facial abnormalities; neural tube defects, such as spina bifida cystica (see Fig. 18-14).
Tetracycline	Stained teeth; hypoplasia of enamel.
Trimethadione	Developmental delay; V-shaped eyebrows; low-set ears; cleft lip and/or palate.
Infectious Agents Cytomegalovirus	Microcephaly; hydrocephaly; microphthalmia; microgyria; mental retardation; cerebral calcifications.
Herpes simplex virus	Microcephaly; microphthalmia; retinal dysplasia.
Rubella virus	Cataracts; glaucoma; chorioretinitis; deafness; microphthalmia; congenital heart defects.
Varicella	Skin scarring; muscle atrophy; mental retardation.
Venezuelan equine encephalitis	Cataracts; brain destruction.
<i>Toxoplasma gondii</i>	Microcephaly; mental retardation microphthalmia; hydrocephaly; chorioretinitis; cerebral calcifications.
<i>Treponema pallidum</i>	Hydrocephalus; congenital deafness; mental retardation; abnormal teeth and bones.
High levels of ionizing radiation	Microcephaly; mental retardation; skeletal malformations.

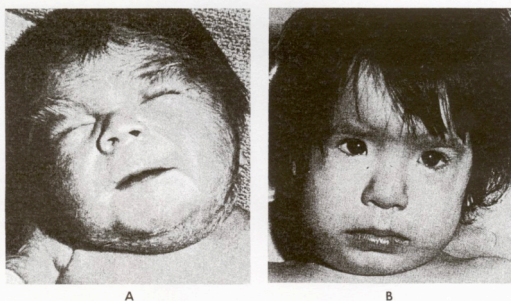
Nicotine

- IUGR
- Premature delivery
- Neurocognitive development

Fetal Alcohol Syndrome

- Characteristic facial features
- Congenital heart disease
- Growth deficiency
- Behavioral/neurocognitive deficits

Fetal Alcohol Syndrome



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- Do you believe her fetus' congenital heart disease was caused by the glass of wine she drank two weeks after conception?

Tetracycline

- Yellow/brown teeth
- Decreased bone growth

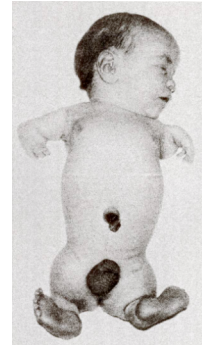
Fetal Hydantoin Syndrome

- Intrauterine growth retardation
- Microcephaly, mental retardation
- Distal phalangeal hypoplasia
- Specific facial features

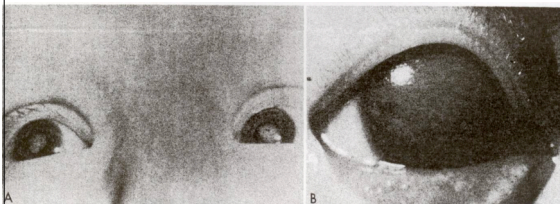
Retinoic acid

- Craniofacial dysmorphisms
- Cleft palate
- Thymic aplasia
- Neural tube defects

Thalidomide Syndrome



Congenital Rubella



Congenital CMV

- Intrauterine growth retardation
- Micromelia
- Chorioretinitis, blindness
- Microcephaly
- Cerebral calcifications, mental retardation
- Hepatosplenomegaly

Ionizing Radiation

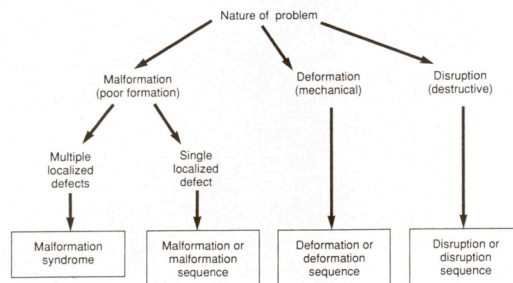
- Affects brain development at 10-18 weeks of gestation a HIGH dose
- No evidence of effect of exposure associated with typical diagnostic studies

Maternal Hyperglycemia

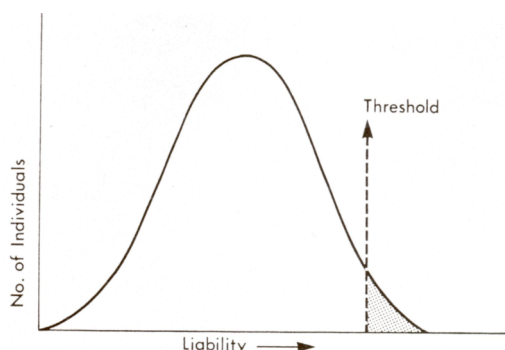
- Congenital heart disease
- Renal, gastrointestinal, and central nervous system malformations such as neural tube defects

Babies of Mother's with PKU

- Mental retardation
- Low birth weight
- Congenital heart diseases



Threshold Effect-Multifactorial



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- After birth, the newborn examination is unremarkable
- The baby's congenital heart disease is repaired
- At age three, the child is growing well and has met all his milestones

- What caused his congenital heart disease?
- What is the risk of recurrence for a future sibling?