Primary prevention of congenital disorders: Avoidance of teratogens

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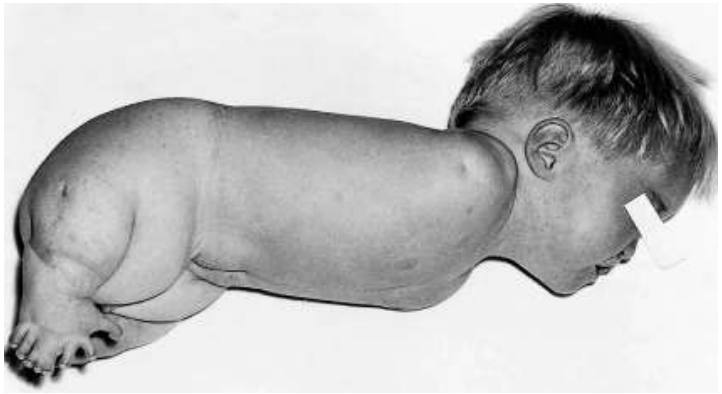
Teratogens

A teratogen is an environmental agent affecting the fetus in utero and may cause a birth defect by interfering with normal embryonic or fetal development

- This presentation gives examples of the most common well known teratogens
- For comprehensive list, consult the references given

Thalidomide

- Thalidomide was used widely in Europe during the years 1958 to 1962 as a sedative. In 1961 an association with severe limb anomalies in babies whose mothers had taken the drug during the first trimester was recognized and the drug was subsequently withdrawn from use. It has been estimated that during this short period over 10 000 babies were damaged by this drug. Review of these babies' records indicated that the critical period for fetal damage was between 20 and 35 days from conception, i.e. 34-50 days after the beginning of the last menstrual period.



Anticonvulsant drugs

Potential fetal effects of anticonvulsant drugs could include:

- Major malformations: The range of effects has been a doubling (for drugs like carbamazepine, phenytoin and lamotrigine) to a 4- to 6-fold increase (for phenobarbital and valproate) in congenital malformations.
- Specific malformations that are more common include cleft lip, cleft palate, heart defects, and spina bifida.

Fetal Alcohol syndrome

- Children born to mothers who have consistently consumed large quantities of alcohol during pregnancy tend to show a distinctive facial appearance, with short palpebral fissures (eye apertures) and a long smooth philtrum (upper lip). They also show mild developmental delay and are often hyperactive and clumsy in later childhood. This condition is referred to as the fetal alcohol syndrome. There is uncertainty about the level of alcohol consumption that is 'safe' in pregnancy and there is evidence that even mild-to-moderate ingestion can be harmful. Generally, it is advised that all women should try to abstain from alcohol intake completely throughout pregnancy.

Isotretinoins

- Use of isotretinoins (e.g., Accutane®) in pregnancy to treat acne can result in miscarriage and birth defects.
- Effective pregnancy prevention should be implemented to avoid unintended pregnancies among women with childbearing potential who use this medication.

Oral anticoagulant: Warfarin

- Warfarin used for the control of blood clotting, has been demonstrated to be a teratogen.
- To avoid exposure to warfarin during early pregnancy, medications can be changed to a non teratogenic anticoagulant before the onset of pregnancy.

Examples of agents with a proven teratogenic effect in humans

Agent	Effect
ACE inhibitors	Renal dysplasia
Alcohol	Cardiac defects, microcephaly, characteristic facies
Chloroquine	Chorioretinitis, deafness
Diethylstilbestrol	Uterine malformations, vaginal adenocarcinoma
Lithium	Cardiac defects (Ebstein's anomaly)
Phenytoin	Cardiac defects, cleft palate, digital hypoplasia
Retinoids	Ear and eye defects, hydrocephalus
Streptomycin	Deafness
Tetracycline	Dental enamel hypoplasia
Thalidomide	Phocomelia, cardiac and ear abnormalities
Valproic acid	Neural tube defects, characteristic facies
Warfarin	Nasal hypoplasia, stippled epiphyses

Reference:
http://mothertobaby.org/

Smoking

- Preterm birth, low birthweight, and other adverse perinatal outcomes associated with maternal smoking in pregnancy can be prevented if women stop smoking before or during early pregnancy.
- Cessation of smoking is recommended before pregnancy.

Maternal Infections

Several infectious agents can interfere with embryogenesis and fetal development. The developing brain, eyes and ears are particularly susceptible to damage by infection.

Teratogenic infections

- Most infections that a woman contracts during pregnancy do not harm the developing embryo or fetus. However, a few infectious diseases can kill an embryo, fetus, or newborn, cause birth defects, trigger a premature delivery, or inhibit fetal growth.
- Nine infectious agents are generally considered to increase the risk of birth defects in humans.
- These include six viruses: **the rubella virus, Venezuelan equine encephalitis virus, cytomegalovirus, varicella zoster virus, herpes simplex viruses, lymphocytic choriomeningitis virus;** and the recently added **Zika virus**.
- One bacterium, **Treponema pallidum**.
- One protozoal parasite, **Toxoplasma gondii.**

Infectious teratogenic agents

Viruses

- Cytomegalovirus: The risk of abnormality is greatest if infection occurs during the first trimester. Overall this virus causes damage in only 5% of infected pregnancies. Effects include chorioretinitis, deafness, and microcephaly.
- Herpes simplex teratogenic effect could include microcephaly and microphthalmia.

Infectious teratogenic agents

Viruses

- Varicella zoster teratogenic effects could be microcephaly, chorioretinitis, and skin defects.
- The rubella virus, which damages between 15% and 25% of all babies infected during the first trimester, causes cardiovascular malformations such as patent ductus arteriosus and peripheral pulmonary artery stenosis. Congenital rubella infection can be prevented by the widespread use of immunization programs based on administration of either the measles, mumps, rubella (MMR) vaccine in early childhood or the rubella vaccine alone to young adult women.

Infectious teratogenic agents

Bacteria

- Syphilis: Congenital syphilis may include hydrocephalus, osteitis, rhinitis.

Parasites

- Toxoplasmosis teratogenic effects may include hydrocephalus, microcephaly, cataracts, chorioretinitis, and deafness. The highest risk for severe effects occurs with maternal infection between 10 and 24 weeks of gestation. Up to 40 percent of fetuses infected during the first trimester of pregnancy develop severe effects.

Teratogenic Physical agents

Ionizing radiation

- Diagnostic radiological studies (less than 0.1 Gy, or 10 rad) that do not expose the embryo (on the head, neck, chest or extremities) will not increase the risk for birth defects or miscarriage above the background risk of 3% for birth defects and 15% for miscarriage (Teratology Primer 2010).
- Exposure of human fetus to high doses (1–2 Gy) of ionizing radiation can result in mental retardation and microcephaly. The most vulnerable stage for the induction of mental retardation and severe microcephaly is reported to be from the 8th to 15th week of human gestation.

Teratogenic Physical agents

Prolonged hyperthermia

There is evidence that prolonged hyperthermia in early pregnancy can cause microcephaly and microphthalmia as well as neuronal migration defects.

It is recommended that care should be taken to avoid excessive use of hot baths and saunas during the first trimester.

Maternal illness

Diabetes mellitus

- The three-fold increase in the prevalence of birth defects among infants of women with diabetes is substantially reduced through proper management at the preconception period and during pregnancy.
- Malformations which occur most commonly in infants of mothers with poor control of diabetes include congenital heart disease, neural tube defects, sacral agenesis, femoral hypoplasia, holoprosencephaly and sirenomelia ('mermaidism').
- The likelihood of an abnormality is inversely related to the quality of the control of the mother's blood glucose levels during early pregnancy.

Hypothyroidism

- The dosages of Levothyroxine® required for treatment of hypothyroidism increase during early pregnancy.
- Levothyroxine® dosage needs to be adjusted for proper neurologic development of the fetus.

Maternal phenylketonuria (PKU)

- Women diagnosed with PKU as infants have an increased risk for delivering neonates/infants with intellectual disability.
- This adverse outcome can be prevented when mothers adhere to a low phenylalanine diet before conception and continueit throughout their pregnancy.

Conclusion

- A large proportion of pregnancies are unintended.
- Most pregnancies are not diagnosed until after the early period of organogenesis.
- Environmental exposures, illnesses, and teratogens can have adverse effects on the fetus very early in pregnancy.
- Chronic disease management and modification of lifestyle behaviors can be adjusted prior to conception.
- Preconception care could protect from these adverse effects by informing, screening and managing couples.