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A REVIEW ON TERATOGENICITY AND ITS CONSEQUENCES

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ABSTRACT

This review give a detail about teratogenecity, its prevention, detection and drugs which cause teratogenesity and some term related wih teratogenesis. Teratogenesis is a effect characterized by structural and functional defects in the developing embryo or foetus. Toxic chemical can kill some of the cell in the blastocyst, resulting in the death of embryo. During the postimplantation period, chemical-induced cell death leads to one of two outcomes. Since organogenesis occurs mostly in the embryonic stages, chemical exposure in the first trimester should be minimized, if possible. Little is known about mechanisms of teratogenesis. In 1941 the first well-documented cases of environmental agents being the cause of severe birth defects were report. As a baby grows in the womb, teratogens may affect parts of the baby's body as they are forming. For example, the neural tube closes in the first 3 to 5 weeks of the pregnancy. Some organs are sensitive to teratogens during the whole pregnancy. This includes the baby's brain and spinal cord.

KEYWORDS: Teratogenicity, Megalocephaly, Blastocyst, Legislation, Malformations, Congenital, Carcinogenesis.

INTRODUCTIONN

Teratogenesis is a prenatal toxicity characterized by structural or functional defects in the developing embryo or fetus. It also includes intrauterine growth retardation, death of the embryo or fetus, and transplacental carcinogenesis (In which chemical exposure of the

mother initiates cancer development in the embryo or fetus, resulting in cancer in the progeny after birth).

Intrauterine human development has three stages: implantation, postimplantation, and foetal development. The first two stages are the embryonic stages and last through the first eight weeks after conception. The fetal stage begins in the ninth week and continues to birth.

Depending on the developmental stage, chemical exposure in the mother can result in different degrees of toxicity in the embryo or fetus. In the preimplantation period, a toxic chemical can kill some of the cells in the blastocyst, resulting in the death of the embryo. During the postimplantation period, chemical-induced cell death leads to one of two outcomes. If death is confined to those cells undergoing active cell division at the moment, the corresponding organs are affected, resulting in malformation. If the cell death is generalized without significant replication by the remaining cells to sustain life, the embryo dies. During the third, fetal, period, chemical injury can retard growth or, if severe enough, kill the fetus.

The genesis of a particular organ (Organogenesis) occurs at a specific time during gestation and is not repeated. Because organogenesis is a tightly programmed sequence of events, each organ system has a critical period during which it is sensitive to chemical injury. Chemical exposure in a critical period is likely to produce malformations of that organ and not others; however, because there is some overlapping of critical periods of organ development and because chemicals frequently remain in the embryo for a period of time, malformations of more than one organ usually occur.

Since organogenesis occurs mostly in the embryonic stages, chemical exposure in the first trimester should be minimized, if possible. Little is known about mechanisms of teratogenesis. It is thought that some teratogens produce malformations directly by killing the cells in the embryo. Teratogens can also produce malformations indirectly by causing maternal toxicity, resulting in oxygen or nutrient deficiency for the embryo. A few well-known examples are discussed below.

Thalidomide is a drug originally marketed to combat nausea and vomiting in pregnancy. It was discovered in the 1960s in West Germany to cause rare limb defects, among other

congenital anomalies. The discoveries about thalidomide triggered legislation requiring teratogenicity testing for drugs.

Chronic alcohol ingestion during pregnancy is the most common cause of congenital problems in mental development. Ingestion of more than 30 millilitres of ethyl alcohol per day during pregnancy can lead to the development of fetal alcohol syndrome, characterized by intrauterine growth retardation and subsequent learning disabilities, such as distractibility, language disorders, and low IQ. Heavier consumption of alcohol, more than 60 millilitres per day, by a pregnant woman can result in malformations of the fetal brain and in spontaneous abortions.

Diethylstilbestrol (DES) is a drug used primarily from the 1940s to the ’50s to prevent miscarriage. The drug is an example of a chemical that can produce Trans placental carcinogenesis. It was discovered in the early 1970s that exposures to diethylstilbestrol before the ninth week of gestation could lead to the formation of rare vaginal and cervical cancers in female progenies.

Etymology

The term was borrowed in 1842 from the French *teratologie*, where it was formed in 1830 from Greek The *teras* meaning "sign sent by the gods, portent, marvel, monster", and -*ologie* (-ology), used to designate a discourse, treaty, science, theory, or study of some topic.

As early as the 17th century, *teratology* referred to a discourse on prodigies and marvels of anything so extraordinary as to seem abnormal. In the 19th century, it acquired a meaning

more closely related to biological deformities, mostly in the field of botany. Currently, its most instrumental meaning is that of the medical study of teratogenesis, congenital malformations or individuals with significant malformations. Historically, people have used many pejorative terms to describe cases of significant physical malformations. In the 1960s David W. Smith of the University of Washington Medical School (one of the researchers who became known in 1973 for the discovery of fetal alcohol syndrome) popularized the term *teratology*. With the growth of understanding of the origins of birth defects, the field of teratology as of 2015 overlaps with other fields of science, including , developmental biology, embryology and genetics.

Until the 1940s teratologists regarded birth defects as primarily hereditary. In 1941 the first well-documented cases of environmental agents being the cause of severe birth defects were report.

History of teratology

Teratology, the study of environment-induced malformations, began as a modern science in the 1930s, with the publication of a set of experiments in which pregnant pigs were fed a diet deficient in vitamin A.

The resulting abnormalities in the offspring demonstrated that mammalian development, by its residence within the mother, was not as protected as was previously believed. In fact, the results of these experiments showed that relatively simple alterations in the environment could have devastating effects on the embryo. The susceptibility of mammalian embryos to toxicity from xenobiotic agents was demonstrated in a series of studies in experimental animals with congeners of biologically important molecules, such as the amino acid mimic azaserine.

A human counterpart to these experiments was reported in the 1950s, when aminopterin was used in some human pregnancies to produce abortion. Several malformed children were born after the drug failed to terminate the pregnancies.

The thalidomide episode of the early 1960s increased our understanding of developmental toxicology by providing an example of an agent that produced minimal toxicity to adults but a high degree of toxicity for the embryo.

Such selective embryotoxicity remains the key element of many experiments evaluating the toxic potential of drugs used during pregnancy. It was during the 1960s that regulatory agencies, including the Food and Drug Administration in the United States, developed requirements for testing drugs in animals before approval for marketing. Drug studies were required to use doses high enough to cause maternal toxicity in order to add confidence that a biologically relevant dose for that species was included in the test protocol. Extrapolation of these results to human beings was initially viewed with skepticism because of the frequent finding of adverse effects in animals with drugs believed to be acceptable for use in human beings. Part of the solution to the difficulties of extrapolating results from animals to human beings is the recognition that maternal disposition (metabolism and distribution) of the drug influences the effect that the drug has on the fetus. Thalidomide is not well absorbed when given orally to rats. Therefore administration of the drug in typical oral teratology studies does not result in a significant dose reaching the embryo. When thalidomide is made soluble in dimethyl sulfoxide and given parenterally, its ability to adversely affect the fetus increases nearly to that observed in rabbits, a species that is very sensitive to thalidomide effects. Modern developmental toxicity studies in animals are performed with an understanding of how each species handles the drug. With the use of current animal testing protocols, drugs that could produce birth defects in human beings should be able to be identified.

The risk stage of pregnancy

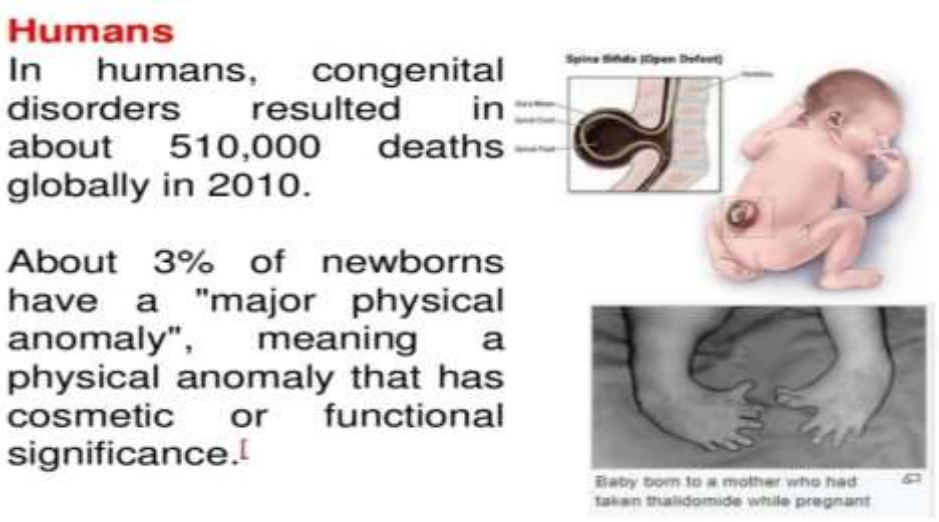
Experts believe that teratogens can begin affecting a baby growing in the womb about 10 to14 days after conception. Conception is when a woman’s egg is fertilized by a man’s sperm. After conception, it takes about 6 to 9 days for the egg to implant in the uterus. Once the fertilized egg is attached to the uterus, the mother and the embryo share a blood supply. Chemicals in the mother's blood can then affect the growing baby.

As a baby grows in the womb, teratogens may affect parts of the baby’s body as they are forming. For example, the neural tube closes in the first 3 to 5 weeks of the pregnancy. During this time, teratogens can cause neural tube defects such as spina bifida. Some organs are sensitive to teratogens during the whole pregnancy. This includes the baby's brain and spinal cord. Alcohol affects the brain and spinal cord, so it can cause harm at any time during pregnancy.

Principles of teratology

- The effect of a teratogen depends on the genetic makeup of the exposed organism.

- Teratogen effects on development depend on timing (Period of 2 – 8 week is particularly sensitive).
- The effect of teratogen may be unique.
- The impact of teratogens may be severe.
- Teratogens differ in how they gain access to the fetus.
- Teratogen dosage is related to degree of abnormal development.



Therapeutic drugs as teratogens

- ACE (Angiotensin converting enzyme-treating high blood pressure).
- Acne medication istretionin (Accuta, Retin-A).

- Alcohol ingested chronically or in binges.
- Androgens (Male hormones).
- Antibiotics tetracycline (Achromycin) and doxycline (Vibramycin) andstreptomycin.
- Anticoagulant (Blood-thinner), warfarin (Coumadin).
- Anticonvulsant (Seizure medications).
- Antidepressant drug lithium (Eskalith, Lithob).
- Antimetabolite/ anticancer drugs methotrexate (Rheumatrex) and aminopterin.
- Antirheumatic agent and metal-binder (Chelator) penicillamine (Ciprimene, depen).
- Antithyroid drugs.
- Cocaine
- DES (Diethylstilbestrol), a hormone.
- Thalidomide (Thalomid) which was approved by FDA for the treatment of a complication of leprosy (Erythema nodosum leprosum).
- Vitamin A and its derivatives including isotretionin, accutane and etretinate- significant riskof many significant anomalies
- ACE inhibitors- may cause kidney damage in the foetus when used in II and III trimester, decrease in the amount of amniotic fluid and deformities of face, limbs and lungs.
- Anticoagulant warfarin- use during I trimester produce defects like hypoplasia and a depressed nasal bridge; termed as foetal warfarin syndrome. Use during II and III trimester is associated with increased risk of foetal malformations.

Heparin	Safe but if taken for long time osteoporosis and decrease in number of platelets in pregnant women occurs
Estrogen and Androgens	Genital tract malformations
Thyroid preparations-	
Methimazole	Overactive and enlarged Thyroid gland
Carbimazole	Overactive and enlarged Thyroid gland
Radioactive iodine	Underactive Thyroid gland in fetus
Propylthiouracil	Safe
Anticonvulsants-	
Carbamazepine	Risk of birth defects
Phenytoin, Phenobarbitone	Bleeding problem in the newborn which can be prevented if pregnant woman takes Vit. K by mouth every day for a month before delivery or if the newborn baby is given an injection of Vit. K soon after birth. Risk of birth defects,

Trimethadione	Increased risk of miscarriage in the women
Sodium valproate	Increased risk of birth defects in fetus; including a cleft palate and abnormalities of the heart, face, skull, hands or abdominal organs
Antidepressants- Lithium	Birth defects (mainly of the heart), lethargy, decreased muscle tone, underactivity of Thyroid gland and nephrogenic diabetes insipidus in the new born. Ebstein's anomaly (tricuspid valve malformation) has been reported in a number of foetuses exposed to this dru

NSAIDs	
Aspirin and other Salicylates	Delay in start of labor, premature closing of ductus arteriosus, jaundice, brain damage in the fetus and bleeding problems in the woman during and after delivery and in the newborn
Antibiotics- Tetracycline	Slowed bone growth, permanent yellowing of the teeth and increased susceptibility to cavities in the body
Chloramphenicol	Gray Baby Syndrome
Ciprofloxacin	Possibility of joint abnormalities (seen in animals)
Kanamycin and Streptomycin	Damage to fetus's ear resulting in deafness (risk of ototoxicity)
Sulfonamides	Jaundice and brain damage in newborn

Antineoplastic agents-	
Busulfan	Birth defects such as less than expected growth before birth,
Chlorambucil	underdevelopment of lower jaw, cleft palate, abnormal development of
Cyclophosphamide	skull bones, spinal defects, ear defects and club foot
Methotrexate	
Oral Hypoglycemic drugs	A very low level of sugar in the blood of newborn. Inadequate control of diabetes in the pregnant woman
Chlorpropamide	

Social Drugs

Alcohol- Foetal Alcohol Syndrome is one of the most serious consequences of drinking during pregnancy. Worldwide incidence of Fetal Alcohol Syndrome is 1:2000 live births.

- Risk of miscarriage almost doubles for women who drink alcohol in any form during pregnancy and birth weight of babies is substantially below normal.
- This syndrome includes inadequate growth before or after birth, facial defects, a small head, mental retardation and abnormal behavioral development. Factors that contribute to the expression of this syndrome are poor nutrition, smoking, drug abuse, genetic disposition and low socio-economic status.

Cigarette smoking- Maternal smoking is one of the few known preventable causes of prenatal morbidity and mortality.

- The most consistent effect of smoking on the fetus during pregnancy is a ***reduction in birth weight***. Birth defects of heart, brain and face are also more common among babies of smokers.
- Risk of sudden infant death syndrome (SIDS), mis-located placenta (placenta previa), premature detachment of placenta (placenta abruptio), premature rupture of the membranes, preterm labor, uterine infections, miscarriages, stillbirths, premature births are increased.
- Changes in uterine and placental oxygenation may be the cause of infant death, prematurity or spontaneous abortions. Therefore all women should be informed of the risk of smoking on the fetus and encouraged to quit smoking during pregnancy

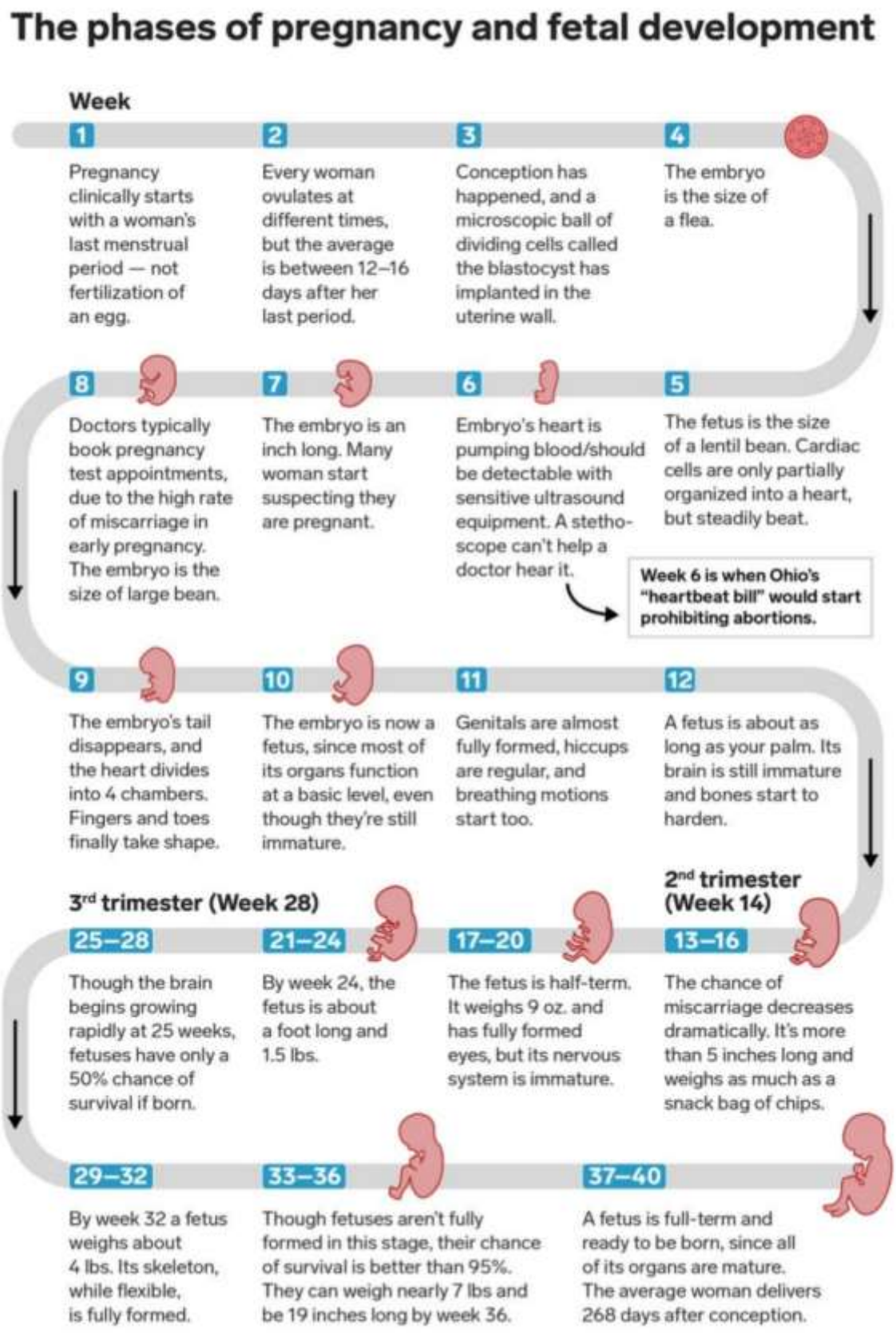
Caffeine- Caffeine is found in various quantities in many beverages, analgesics, diet aids and stimulants, Hence it is the most commonly ingested drug during pregnancy.

- Evidence suggests that consuming caffeine during pregnancy poses little or no risk to the fetus. Caffeine contained in coffee, tea, some sodas, chocolates and some drugs is a stimulant that readily crosses the placenta to the fetus.
- If taken in **high dose** it may stimulate the fetus increasing heart and breathing rate .
- Caffeine also may decrease blood flow across placenta and decrease the absorption of iron; increasing risk of anemia.

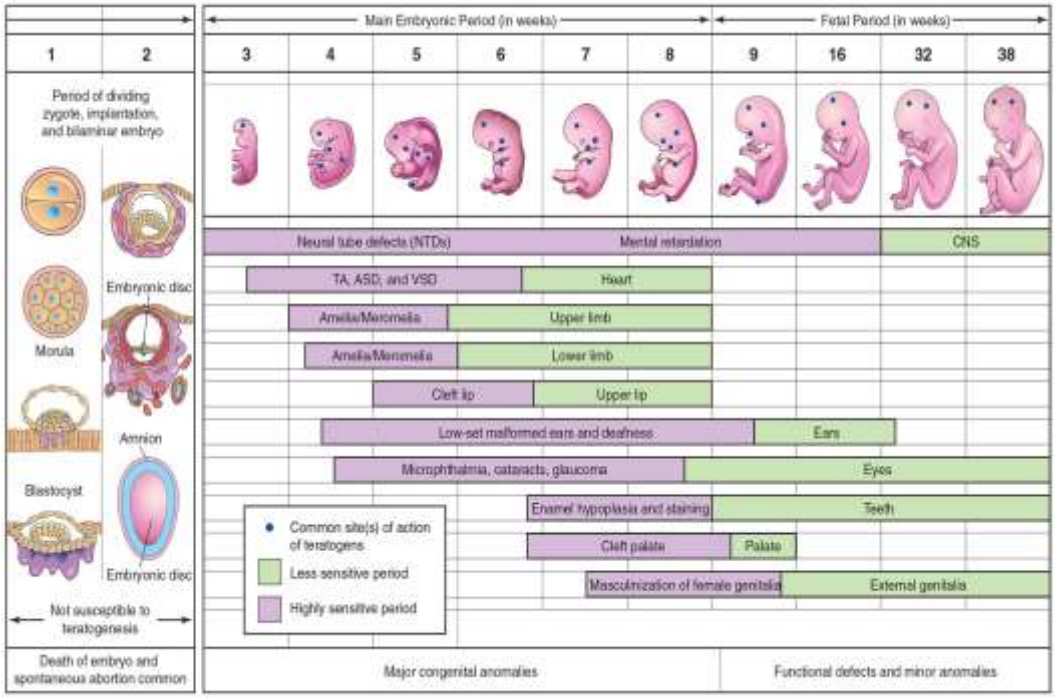
ILLICT drugs- Use of illicit drugs like cocaine and opioids during pregnancy can cause complications and serious problems in the developing fetus and the newborn.

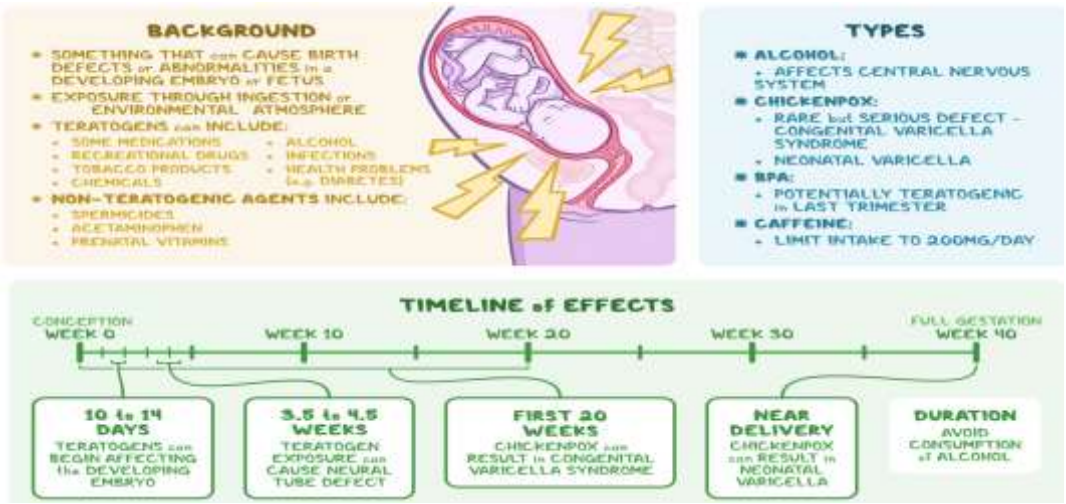
- Growth of fetus is likely to be inadequate and premature birth defects are more common.
- Cocaine crosses the placenta, constricts the blood vessels reducing blood flow to the fetus. The reduced blood and oxygen supply to the fetus slows the growth of bones and intestine.
- Use of cocaine can also cause complications during pregnancy. Among women who use cocaine throughout pregnancy, 31% have preterm delivery and 15% have premature detachment of placenta. The chances of miscarriage also increase

Growth and Development



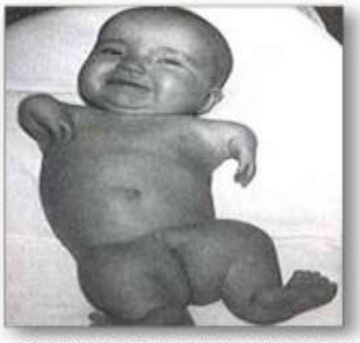
Teratogens and Their effects



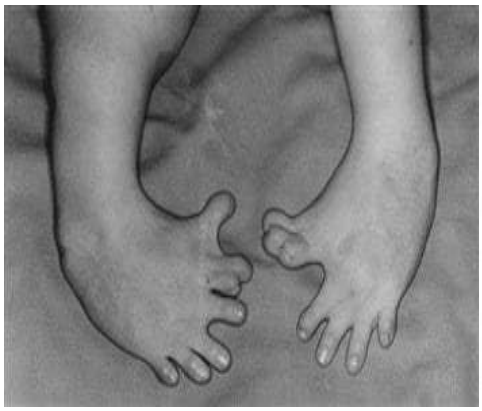


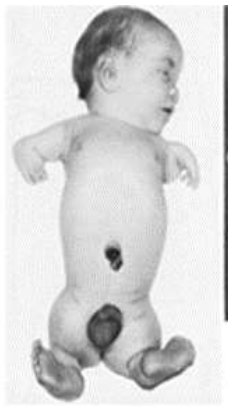
Thalidomide

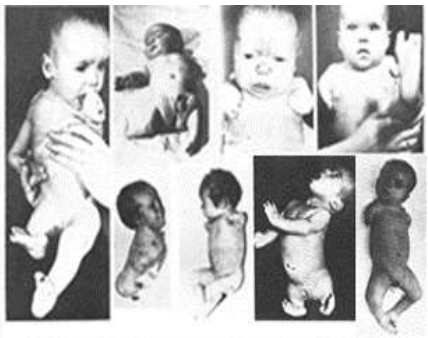
- Thalidomide was meant as a sleeping aid but prescribed to pregnant women to treat anxiety and nausea
- The drug caused serious birth abnormalities for hundreds of children[50]
- Mothers of thalidomide babies felt responsible for the conditions of their children
- Thalidomide led to stricter tests to determine a drug's impact on a fetus



An infant with birth abnormalities from thalidomide







Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

Survey report

S. no.	Teratogenic drugs	Drug and Brand name	Available strengths (in mg)	Teratogenic effects of drugs
1.	ACE (Angiotensin converting enzyme) Inhibitors. (Teratogenic in second and third trimesters of pregnancy)	Benazepril (Lotensin)	5mg,10mg, 20mg, 40mg	ACE inhibitors produce a fetopathy by inhibiting fetal urine production. Fetopathy include renal dysplasia and renal failure and intrauterine growth retardation. It increased infant risks for cardiovascular and nervous system anomalies.
		Captopril (Capoten)	25mg,50mg,100mg	
		Enalapril (Vasotec)	2.5mg,5mg,10mg	
		Fosinopril sodium (Monopril)	10mg,20mg,40mg	
		Lisinopril (Zestril, Prinivil)	5mg,10mg,20mg, 40mg	
		Ramipril (Altace)	1.25mg,2.5mg,5mg	
2.	Acne medication (Isotretinoin)	Isotroin	10mg,20mg,30mg	Isotretinoin is a potent human teratogen. It increased risk for congenital defects
		Accutane	10mg,20mg,40mg	

		Tufacne	10mg,20mg	in infants exposed to the drug in utero, including craniofacial, cardiovascular, neurological and thymic malformations.
		D`Acne	10mg,20mg	
		Glotret	5mg,10mg	
3.	Antibiotics	Tetracycline (Acromycin)	250mg,500mg	Birth defects include-Brain malformations, heart defects, hearing loss, hypoplasia, and cause discoloration of long bone and teeth.
		Doxycycline (Vibramycin)	50mg,75mg,100mg	
		Streptomycin (Ambistryn)	750mg, 1000mg (injection)	
		Sumycin	250mg, 500mg	
4.	Thalidomide	Thalomid	50mg,100mg,150mg	Babies born with malformations such as Amelia, phocomelia, bone hypoplasia and absence of bones.
		Thaloma	50mg, 100mg	
5.	Anticoagulant (blood thinner)	Warfarin (Coumadin)	1mg,2mg,2.5mg, 3mg,4mg,5mg	Increased rates of fetal loss. Internal bleeding of the fetus, lower bone growth.
6.	Anticonvulsants	Phenytoin (Dilatin)	50mg,100mg,200mg	Congenital heart disease, cleft lip/palate, urogenital and neural tube defects, skeletal abnormalities.
		Valproic acid (Valprotate)	100mg, 250mg	
		Trimethadione (Tridione)	300mg,600mg	
		Carbamazepine (tegretol)	100mg,200mg	
7.	Anticancer drugs	Methotrexate (Rheumatrex)	2.5 mg	These drugs target vital cellular functions of embryo.
		aminopterin	25mg,50mg	

CONCLUSION

The unique nature of physiology of pregnancy presents challenges for pharmaceutical treatment of chronic and acute disorders and for symptom management of many complaints associated with pregnancy. It is the responsibility of all clinicians including pharmacists to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. Counseling women who have had exposure to drugs

about risk of teratogens involves accurately identifying exposure and quantifying the magnitude of exposure. This may be straightforward for prescribed drugs but it can be much more difficult with ethanol or other illicit substances or OTC drugs. Also when selecting drugs to be used in pregnancy effectively, drugs that have been in use for a long time are often preferable because fetal safety has been established even though newer alternatives may be available.

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