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Review Paper

Teratogenic Effect of Different Drug at Different Stage of Pregnancy

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ABSTRACT

The process by which congenital malformation are produced in an embryo or fetus .It is also known as teratogenesis. The beginning and growth of an embryo from a physical cell (physical embryogenesis) or a zygote (zygotic embryogenesis). Another name for it is the organogenesis era. Three trimesters make up a gestation's nine-week lifespan. Because all of the medications a woman takes have the potential to create harmful effects in the developing foetus or nursing infant, pregnancy and lactation represent a specific clinical scenario where medication therapy is particularly concerning. The first trimester of pregnancy is when medications are most effective. All women who are at risk of becoming pregnant should have common ailments treated with attention, as this time is crucial before a gestational opinion is formed. A birth deformity complicates about three to five out of every live birth.A birth deformity complicates about 3–5 out of every 5 live births, which adds up to about a thousand kids. Teratogenicity, microcephaly, hydrocephalus, spina bifida, and colourful runs are among the defects caused by colourful medications such tetracycline, warfarin, thalidomide, and chlorramphenicol.

INTRODUCTION

Approximately two-thirds of pregnant women take at least one medication during pregnancy, with over 60% of pregnant women taking a prescription [1] Teratogenic effects have been clearly demonstrated for only about 30 prescription drug treatments in humans [Webster and Freeman, 2003], but pregnant women and their physicians are frequently concerned about the possibility that a treatment that may be needed to improve a woman's health may harm her developing embryo or fetus. Although it is only prudent to avoid unnecessary medication use in pregnancy,

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gratuitous fear of damaging the embryo may itself be harmful, as avoiding needed treatment for maternal illnesses like diabetes mellitus, depression, or hypertension can endanger both the mother and the fetus. [2] Any substance that results in abnormalities after fetal exposures during pregnancy is considered a teratogen. Teratogens are typically identified following a rise in the incidence of a specific birth abnormality. The stage of embryonic development when organogenesis occurs Teratogens, active agents in drugs, can cause birth defects or anomalies in fetuses during pregnancy. Teratology studies their occurrence, progression, and origin, considering factors like exposure duration, teratogenic material quantity, and developmental stage. [3]

Teratogenicity: capacity of a drug to cause fetal abnormalities when administered to the pregnant women. The induction of malformation by teratogens. Teratogenicity testing come in to being since the tragedy of 1961.

Teratology: Branch of science which studies the mechanism and pattern of abnormal development. It is a sub-discipline in medical genetics which focuses on the classification of congenital abnormalities in dysmorphology. Drugs, alcohol, chemicals and toxic substances are examples of teratogens. Teratogens can also increase the risk for miscarriage, preterm labor or still birth. Teratology started as a descriptive science, stemming from a variety of mystical and scientific theories explaining the etiology of congenital malformations, such as maternal impression, the position of the stars, hybridization, etc.

Teratogenesis: The process by which congenital malformation are produced in an embryo or fetus.
Teratogen: An agent that can produce a permanent alteration of structure or functions in an organism exposed during embryonic or a fetal life. A teratogen is a substance that interferes with normal fetal development and causes congenital disabilities. Drugs, alcohol, chemicals and toxic substances are examples of teratogens. Drugs, medicine, chemicals, certain infections and toxic substances are examples of teratogens. Teratogens can also increase the risk for miscarriage, preterm labor or stillbirth. Teratogens are substances that can harm the fetus during pregnancy. Studies have shown that teratogens cause congenital disorders and increase the chance for miscarriage, stillbirth or other pregnancy complications.

Pregnancy-

Pregnancy is the period in which an egg cell is fertilized by a sperm to form a new cell, called the zygote, that eventually develops into a new human organism, to be born. The period of human pregnancy is 40 weeks from the date of the last menstrual period (LMP), or 38 weeks from the time of conception, on average. Just over the 9 months. [4]

Stages of pregnancy: Pregnancy is divided into four stages.

- The first stage of pregnancy is the slow opening of your cervix.
- The second stage is the birth of your baby.
- The third stage is separation and birth of the placenta.
- The fourth stage is the first two hours after birth.

Trimesters of Pregnancy

First Trimester (0 to 13 Weeks) The first trimester is the most crucial to your baby's development. The first trimester begins with the start of gestational age as described above, that is, the beginning of week 1, or 0 weeks + 0 days of gestational age (GA). It ends at week 12 (11 weeks + 6 days of GA or end of week 14 (13 weeks + 6 days of GA)

Second Trimester (14 to 26 Weeks) The second trimester is defined as starting, between the beginning of week 13 (12 weeks +0 days of GA and beginning of week 15 (14 weeks + 0 days of GA.It ends at the end of week 27 (26 weeks + 6 days of GA)] or end of week 28 (27 weeks + 6 days of GA)

Third Trimester (27 to 40 Weeks) The third trimester is defined as starting, between the beginning of week 28 (27 weeks + 0 days of GA) or beginning of week 29 (28 weeks + 0 days of GA)

During the third trimester of pregnancy [5]

- Itching caused by the stretching of the skin.
- Burning sensation in due to indigestion and increase acid reflux Weight gain in the third trimester of pregnancy is the most common symptom as your baby is getting ready for birth.
- Constipation or loose motions in the third trimester of pregnancy is also very common
- If it continues, do consult your doctor Increase fatigue caused by the body growing to accommodate baby and carrying the extra weight of baby.
- Vomiting during the third trimester.

Principle of Teratology:

Games Graves Wilson gives six principals of teratology. In considering the effects of drugs on pregnancy, it is important to remember the 6 principles of teratology: Although teratogenic exposures account for a very small percentage of all birth defects, there are approximately 3 million persons in the United States today living with the consequences of developmental defects caused by in utero exposure to teratogens. It is important to remember that nearly all teratogen-induced birth defects are preventable, if we understand the 6 basic principles of teratology [6]

1. genetic susceptibility
2. development stage
3. mechanisms
4. end points
5. access
6. dose response.

Principle 1: Susceptibility to teratogenesis depends on the genotype of the concepts and the manner in which it interacts with the environment. Susceptibility to teratogenesis depends on the genotype of the conceptus (The conceptus includes all structures that develop from the zygote, both embryonic and extraembryonic. It includes the embryo as well as the embryonic part of the placenta and its associated membranes - amnion, chorion, and yolk sac) and the manner in which this interacts with adverse environmental factors.

Principle 2: Susceptibility to a teratogenic agent varies with the developmental stage at which the exposure occurs. Susceptibility to teratogenesis varies with the developmental stage at the time of exposure to an adverse influence. There are critical periods of susceptibility to agents and organ systems affected by these agents.It is a basic biologic precept that developing organisms are more sensitive to change than are mature, fully developed organisms. This implies that he developmental span of the embryo, although not necessarily at a constant rate.

Principle 3: Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis) Teratogenic agents act in specific ways on developing cells and tissues to initiate sequences of abnormal developmental events. The term mechanism refers to the early, and often the first, event in a series of intervening events between cause and an effect. The initial event is possibly the most important of the series, not only

because it is the connecting link between the cause and the physiologic changes that follow but also because it very likely influences the nature of these latter changes.

Principle 4: The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder. The access of adverse influences to developing tissues depends on the nature of the influence. Several factors affect the ability of a teratogen to contact a developing conceptus, such as the nature of the agent itself, route and degree of maternal exposure, rate of placental transfer and systemic absorption, and composition of the maternal and embryonic/fetal genotypes.

Principle 5: Access of an adverse environmental agent to developing tissues depends on the nature of the agent (Influences) There are four manifestations of deviant development (Death, Malformation, Growth Retardation and Functional Defect).

Principle 6: The manifestations of deviant development increase in degree as dosage increases from the no-effect to the lethal level. Manifestations of deviant development increase in frequency and degree as dosage increases from the No Observable Adverse Effect Level (NOAEL) to a dose producing 100% Lethality (LD100). There is a dose-response relationship for teratogens and teratogenic activity, as there is for drugs and therapeutic effect. It is important to consider this principle as it relates to thresholds for various toxicologic effects. For regulators attempting to define drug or product safety, the no-effect or threshold level for adverse effects is considered to be a critical benchmark. [7]

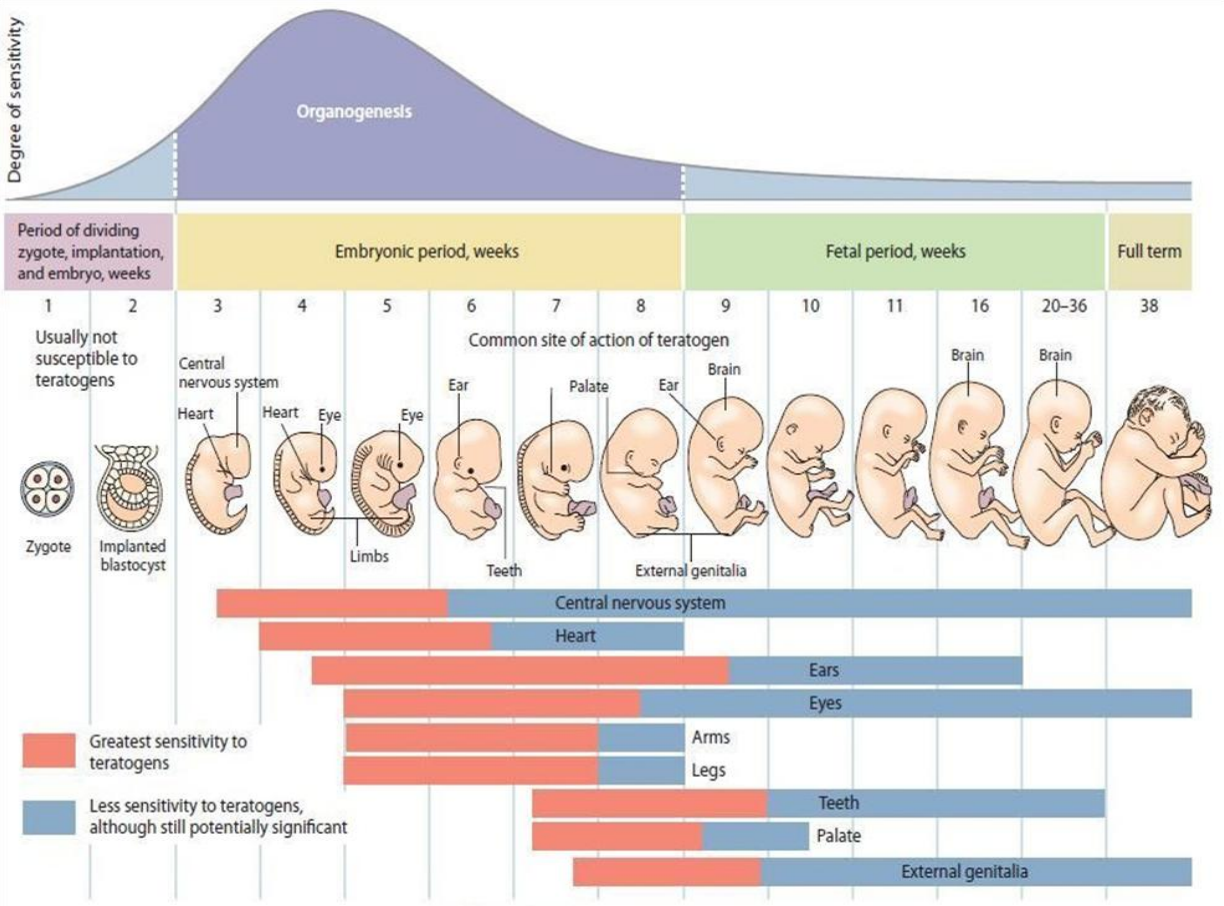

Fig.1 Teratogen and the timing of their effect of prenatal development

Teratogenic drug

1. Thalidomide
2. Epileptic drug (Valproic Acid / Phenytoin)
3. Retinoid (vitamin A)
4. Third elements (Lithium)
5. Warfarin
6. Alcohol
7. Cocaine
8. Tetracycline

Teratogenic drug and their effect on fetus:

Table. No -1 Teratogenic drug and their effect on fetus:

Sr.No.	Drug	Effects of Fetus/ Offspring
1.	ACE inhibitor	Foetal loss Growth retardation Renal damage
2.	Anti-cancer drug	Foetal death Hydrocephalus Multiple defects
3.	Aspirin	Premature closure of the ducts arteriosus
4.	Thalidomide	Phocomelia Absence long bone of the limbs Absence of external Multiple defect
5.	Warfarin	Eye and hand defect Growth retardation CNS malformation

List of some of the drugs whose use is contraindicated during pregnancy which may affects they may produce on the fetus.

Thalidomine and Pregnancy:

In 1957, thalidomine was first put on the market in Germany.The medication was sold by the German pharmaceutical business. Primary was prohibited because thalidomide, a sedative or hypnotic, was also said to be therapeutic. "tension, gastritis, anxiety, and insomnia"Later on, it was used to treat nausea and to help pregnant women who were experiencing morning sickness.In Germany, thalidomide quickly became an over-the-counter medication for 5,000–7,000 infants. Focomelia, or limb deformity, during birth Of these children, only 40% made it out alive.Approximately 10,000 instances were documented worldwide. Out of 10,000, just half made it out alive.Deformed hearts and eyes, distorted digestive and urinary systems, blindness, and hearing were among their consequences.[8]

Fig.2 Thalidomode syndrome

Warfarin and pregnancy:

Warfarin is not recommended during pregnancy as it can sometimes cause birth defects and bleeding problems for the baby. Warfarin use in I trimester produces blights like nasal hypoplasia and a depressed nasal ground; nominated as Fetal Warfarin Pattern and also use during II and III trimesters is associated with increased threat of fetal deformations. Warfarin, which is considered the first- line remedy for thrombosis prophylaxis outside gestation, readily crosses the placenta and renders the fetus unfit to synthesize vitamin K-dependent proteins. [9]

Teratogenic effect: robotic revocations; can beget the fetal warfarin pattern (cadaverous abnormalities, nasal hypoplasia, narrow nasal ground, scoliosis, spinal calcifications, femur and heel bone calcifications, low birth weight, and experimental disabilities.

Fig.3 Fetal warfarin syndrome

3. ACE Inhibitor

ACE inhibitor or ARB exposure in early pregnancy was associated with a higher risk of major congenital malformations (odds ratio [OR] 1.82, CI 1.42-2.34), cardiovascular malformations (OR 2.50, 95% CI 1.62-3.87), and stillbirths (OR 1.75, 95% CI 1.21-2.53), whereas pregnancies exposed. The use of an ACE inhibitor during the second and third trimesters of pregnancy has been associated with a number of serious foetal malformations including oligohydramnios, foetal and neonatal renal failure, bony malformations, limb contractures, pulmonary hypoplasia, prolonged hypotension and neonatal death. [10]

ACE Inhibitor Side Effects

- Cough
- Angioedema / Agranulocytosis
- Proteinuria / Potassium excess (hyperkalemia)
- Taste change
- Orthostatic hypotension
- Pregnancy contraindication (fetal renal damage)
- Renal artery stenosis contraindication
- Increases renin
- Leukopenia / Liver toxicity

4.Phenytoin

Phenytoin is a medication used to treat epilepsy (seizure disorder). If phenytoin is taken by the mother in the first trimester, there is approximately a 5 to 10 percent chance that the baby could be born with a combination of birth defects known as the Fetal Hydantoin. [11,12]

5.Alcohol

Drinking alcohol during pregnancy increases the risk of miscarriage, premature birth and your baby

having a low birthweight. It can also affect your baby after they're born. Drinking during pregnancy can cause your baby to develop a serious condition called foetal alcohol spectrum disorder (FASD). There is no known safe amount of alcohol use during pregnancy or while trying to get pregnant. There is also no safe time for alcohol use during pregnancy. All types of alcohol are equally harmful, including all wines and beer.FASDs are preventable if a baby is not exposed to alcohol before birth. [13]

Children with FASDs might have the following characteristics and behaviors:

- Abnormal facial features, such as a smooth ridge between the nose and upper lip (this ridge is called the philtrum)
- Shorter-than-average
- Small head size
- Low body weight
- Hyperactive behavior
- Difficulty with attention
- Poor memory
- Learning disabilities
- Speech and language delays
- Intellectual disability or low IQ
- Poor reasoning and judgment skills
- Sleep and sucking problems as a baby
- Vision or hearing problems
- Problems with the heart, kidney, or bones

6. Cocaine:

Cocaine is a powerful stimulant with a high potential for misuse and is classified as a Schedule II drug. Although prescription cocaine has limited applications as a vasoconstrictor and an early anaesthetic, its use develops illegally. Cocaine use during pregnancy can affect the growing embryo and foetus in a number of ways, ranging from severe cardiac and gastrointestinal problems to premature death because to inadequate blood flow. These substances form a teratogen and cause blights in foetuses during prenatal development. [13,14]

Action Mechanism: Because of its vasoconstrictor effects, cocaine may cause the fetus's blood flow to stop. When someone uses cocaine, the time it takes for them to feel its goods depend on the system of ingestion. Edging in and smoking.

7.Tobacco: One of the primary preventable causes of adverse health outcomes during pregnancy, including preterm birth, low birth weight, and delivery, is tobacco use. Nonetheless, the dangers of smoking while pregnant are well known, 16 of Among the highest rates in the western world, all pregnant Danish women smoked in 2005. In tobacco Pregnancy can also result in natural abnormalities, most likely due to a teratogenic impact.

Action Mechanism:

Because nicotine reduces the perfusion of embryonic tissues, it acts as a vasoconstrictor that hinders intrauterine growth. could result in abrupt placental birth. Additionally, the carbon monoxide found in cigarette smoke crosses the placenta, generating

7.Antibiotic –Tetracycline:

Tetracyclines are teratogens due to the liability of causing teeth discolouration in the fetus as they develop in immaturity. For this same reason, tetracyclines are contraindicated for use in children less than 8 times of age. Some grown-ups also witness teeth abrasion (mild slate tinge) after use. Teratogenic effect: Impaired teeth and bone development, Yellow brown discoloration of teeth [15]

CONCLUSION

Analysing and taking into account the risks of gonadotoxic medicines, mother physiology, and foetal risk throughout all trimesters is necessary when using pharmaceuticals during pregnancy. The safest medication should be used for less serious conditions. The chance of teratogenic adverse effects may be overshadowed by the risk of morbidity or mortality in life-threatening illnesses. But the safest medication should be given once the disease is stable. Knowing how teratogenesis occurs is crucial for preventing such occurrences, identifying those at risk early, and developing treatment plans. Experimental teratology provides information on normal development by illuminating pathways that may be compromised by substances like medications, genes, or environmental factors.

REFERENCES

1. Luke D Starling, 1 Ashutosh Sinha, 2 Duncan Boyd, 3 and Anke Furck Fetal warfarin sy Alwan S, Polifka JE, Friedman JM. b. Addendum: Sartan treatment during pregnancy. Birth Defects Res a Clin Mol Teratol 2005,73:904–905.
2. Alwan S, Polifka JE, Friedman JM. a. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res a Clin Mol Teratol 2005,73:123–130.
3. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Roblin D, Smith DH, Yood MU, Morse AN, Platt R. 2004. Prescription drug use in pregnancy. Am J Obstet Gynecol 2004,191:398–407.
4. Punam Sachdeva, B. G. Patel, and B. K. Patel1 Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb
5. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med. 2006; 354:2443– 2451
6. Wilson JG. Current status of teratology. General principles and mechanisms derived from animal studies. In: Handbook of teratology. New York, NY: Plenum Press;1977;1:47-58
7. Błaszczyk B, Miziak B, Pluta R and Czuczwar SJ: Epilepsy in pregnancy-management principles and focus on valproate. International Journal of Molecular Sciences 2022; 23(3): 1369.
8. Hansen JM, Harris C. A novel hypothesis for thalidomide-induced limb teratogenesis: redox misregulation of the NF-kB pathway. Antioxid Redox Signal 2004; 6:1 – 14
9. Songmen S, Panta OB, Paudel SS and Ghimire RK: Chondrodysplasia punctata: A Case Report of Fetal Warfarin Syndrome. Journal of Nepal Health Research Council 2017; 15(1): 81-84
10. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Engl J Med 2006; 354:2443– 2451.
11. 11 Finnell RH, Dansky LV. Parental epilepsy, anticonvulsant drugs and reproductive outcome: epidemiological and experimental findings spanning three decades. I. Animal studies. Reprod Toxicol 1991; 5:281-299.
12. Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs andreproductive outcome: epidemiological and experimental findings spanning three decades. II. Human studies. Reprod Toxicol 1991; 5:281-298.
13. 13 Stacy Mosel, L.M.S.W.: Sco Thomas, MD Dangers of Using Cocaine During Pregnancy Sep 14, 2022
14. Robert E. Arendt, PhD, Sonnia Minnes, and Lynn T. Singer Fetal Cocaine Exposure:

Neurologic Effects and Sensory-Motor Delays1996 Jan.

15. 16 Mathew JL: Effect of maternal antibiotics on breast feeding infants. Postgraduate Medical Journal 2004; 80(942): 196-200.

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