WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Teratogenic Effect of Various Drugs at Different Stage of Pregnancy

Miss. Prajakta Vilas Patil[1], Mr. Yashwant Sanjay Ahire[2], Mr. Anurag Chhaju Kumavat[3], Mr. Abhishek Shyam Amrutkar[4], Mr. Nilesh Ramesh More[5], Mr. Pritam Santosh Gavali[6], Mr. Tejas Ishwar Wagh[7].

[1,2,3,4,5,6,7]Dr. Uttamrao Mahajan college of B pharmacy Chalisgaon

ABSTRACT

Drugs that can cause birth defects are said to be teratogenic drugs. Teratogenesis is the procedure of cause malformations or birth weakness in the fetus or embryo. Approximately 3% of newborns suffer from some type of birth defect. Teratogenesis is caused by teratogens.

1. INTRODUCTION

Teratogenicity is the ability of substances, organisms, or physical agents to alter the course of embryonic or fetal development. A Teratogens are usually found after a specific event has occurred. For example, in the early 1960s, a drug called thalidomide was used to treat morning sickness, which is when organogenesis occurs.

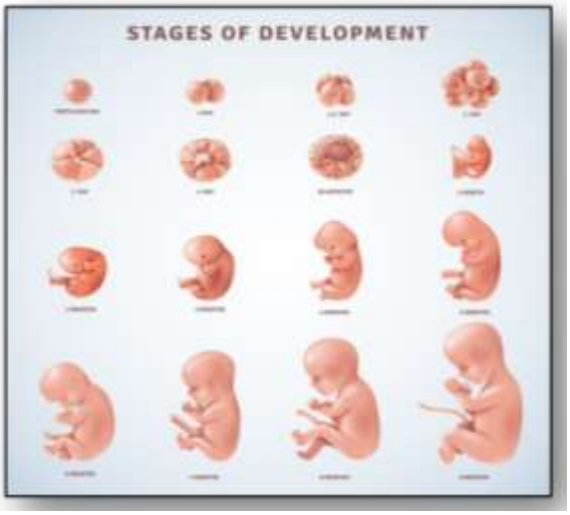
1.1 DEVELOPMENT OF PREGNANCY

There are four stages of development during pregnancy in every woman which are follow:

1) Fertilization
2) Blastocyst development
3) Embryo development
4) Fetus and placenta development.

1.2 DRUGS AND BIRTH DEFECTS

All aspects of human developmental abnormalities must be considered when evaluating the effects of teratogens. Symptoms may be caused by an unknown or genetic background. It is known that 25% of these have genetic (chromosomal, Mendelian, etc.) roots. Although the cause of approximately 65% of abnormalities is unknown, they may be caused by genetic and environmental factors (polygenic/multifactorial). Almost anything parents use during pregnancy has the potential to harm the fetus and cause anatomical abnormalities (teratogens). Almost all fat-soluble substances pass through the placenta without problems. When a substance has a low molecular weight, it can move more easily in water. The amount of drug that freely crosses the placenta is also affected by the amount of drug bound to plasma proteins. Most drugs cross the placenta to some extent, except for large organic ions such as insulin and heparin (fractionated and continuous).



ARIABLES AFFECTING TERATOGENESIS

DOSAGES

Although it is generally known that high doses of teratogens are more dangerous than low doses, this is not always the case. The embryo can respond to a teratogen at any time in one of three ways: (1) low doses have no effect; (2) a range of physical disorders may occur with small doses; (3) high dose Embryo will be killed and will not cause any specific teratogenic effects. Teratogens affect animals in very small doses; It is usually one-third to one-half the dose that kills the mother. The stage of development of the given drug may affect the results. In other words, a substance is teratogenic only at a certain dose or level. Similarly, an agent may be teratogenic but not lethal at a single dose, and may be lethal or teratogenic at varying levels.

1.3 STAGES OF EMBRYONIC DEVELOPMENT

It is important to determine when potential teratogens emerge during fetal development. Three exposure phases with different times for each body can be distinguished. (1) During the first few weeks of life, perhaps two weeks after pregnancy in humans, embryos are resistant to teratogenicity damage. 2 Although severe trauma can kill the embryo, most survivors have no physical abnormalities. This is probably because early embryonic cells are not yet irreversibly differentiated. If one phone is broken, the other surviving phone will be taken.

(2) Organogenesis, the process of organ differentiation, occurs in the human body mainly between the 3rd and 8th weeks of the embryo (5-10 weeks of menstruation); However, differentiation between the brain and gonads is rare. Susceptibility to teratogens peaks during organogenesis. Teratogens have unique effects; They may affect one system of an organism at one stage of development and another system at a different stage. Therefore, the exact time of injury affects whether a deformity occurs and the reality of the deformity.

(3) The main feature of embryonic development after organogenesis is the size of the body. This period begins between 8 and 10 embryonic weeks for most of the human body. Teratogens can affect the size of organs or the overall development of the embryo during this period. Obvious defects, on the other hand, cannot be foreseen. For example, giving androgens to pregnant women after the 12th week will increase the growth of the female fetus but will not alter the opening of the urethra or the fusion of the labial folds. Generally speaking, drugs that are harmful to newborns will also be harmful to older fetuses. Abnormalities may also be the result of side effects.

1.5 GENOTYPE

There are two genetic methods that can explain the difference in genetic diversity: polygenic inheritance and monogenic or Mendelian inheritance. Differences in drug use and subsequent teratogenic susceptibility may be polygenic between individuals. In polygenic combinations, many genes can work together to affect a particular trait. In terms of genetic responsibility, genotypes cause permanent variation. This process becomes most meaningful when considering the three levels of drug catabolism (maternal ability to absorb or metabolize the teratogen, placental transfer, and fetal metabolism). The chemical processes of adult twins are more similar than twins, but not enough to be explained by a single gene. However, single gene factors exist. A single mutation in a minority of people can make them particularly susceptible to sensitivity or resistance to certain drugs. We call these people as having pharmacogenetic diseases. Examples include pseudocholinesterase deficiency, resistance to the blood thinners warfarin and heparin, and the inability to catabolize (decarboxylate) drugs such as hydralazine or isoniazid. In contrast, the mutated allele prevents the fetus from neutralizing potential teratogens. Therefore, administration of a specific teratogen may affect the fetus but not other (normal) fetuses.

1.6 DRUG INTERACTION

When two teratogens are administered simultaneously, the effects may differ from the effects when the drugs are administered alone. For example, folic acid can inhibit cortisol-induced teratogenesis in rats, possibly by stimulating enzyme systems to digest the teratogen or by competing with it for binding

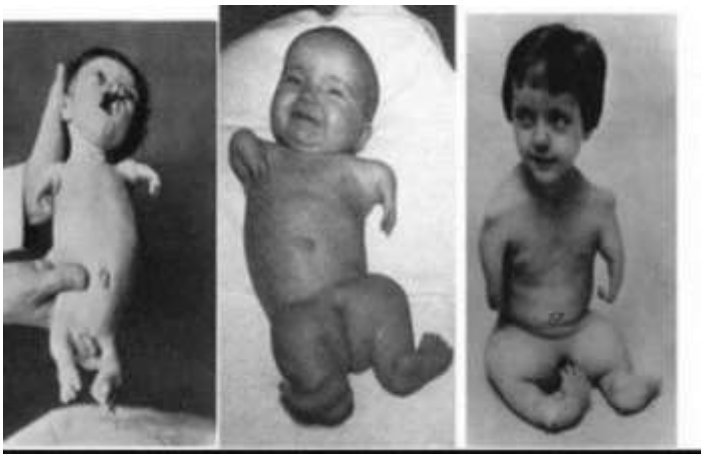
sites. On the other hand, a substance may increase the teratogenic potential of another substance. For example, the food preservative benzoic acid increases the teratogenicity of aspirin in rats. Inhibition of the enzyme, removal of enzyme-producing cells, and saturation of the binding site of the carrier protein are methods that will reduce the concentration of unbound active teratogens, if present.

EFFECTS OF THERAPEUTIC DRUGS

THALIODOMIDE

In the 1960s, thalidomide was used as a treatment. It causes deformed penis, facial hemangioma, esophagoduodenal atresia, heart defects (such as tetralogy of Fallot), renal hypoplasia, urinary tract abnormalities, genital defects, dental abnormalities, ear abnormalities, facial nerve paralysis. Rare cases of cleft palate do not affect the central nervous system. Children are moderately intelligent. 23 to 28 days after conception is a sensitive window for the occurrence of thalidomide birth defects, with 14 days being a critical window. At this time, approximately 20% of pregnancies result in abnormalities in the babies; The most prominent limb deformities are 6 or 7 toes of each foot, ranging from three to four digits, usually with preaxial polydactyly. or thallus deformity of the upper and lower extremities. The origin of the deformity in the limb is related to the neural crest-based scleral tissue, McCready said. McCready and colleagues Erosion expanded their study of visceral anomalies in infants who died of various congenital anomalies, limb longitudinal anomalies, by attempting to determine whether damage to the neural crest affects the development of patterns derived from sensory autonomic nerves derived from damaged areas of the neural crest. mistake. When autopsy data were used for scleral and visceral maps, neuroanatomical connections were found in 89% of patients. The authors hypothesize that developmental connections are present in many congenital anomaly syndromes in the form of neural remnants or embryonic developmental responses with common regional innervation. Thalidomide inhibits angiogenesis and its teratogenicity is associated with its anti-angiogenic effect.

THALIDOMIDE EFFECT ON FETUS



FOLIC ACID DEFICIENCY AND FOLIC ACID ANTAGONISTS

Many women who give birth to children with neural tube defects (NTDs) have been found to be folate deficient; folate antagonists can also cause NTDs. Up to 70% of NTDs, especially anencephaly, are caused by folate deficiency. The US Food and Drug Administration (FDA) recommends adding adequate amounts of folic acid to foods to support their nutritional value. A daily dose of 0.4 mg of folic acid, usually found in multivitamin stores, reduces the risk of periconceptional NTDs by approximately 60%. To reduce the risk of spina bifida or other NTDs during pregnancy, the U.S. Public Health Service recommends that all U.S. women of childbearing potential who take 0.4 mg of folic acid each day during pregnancy be careful to limit their intake to 0.4 mg of folic acid each day during pregnancy. Taking 1 mg of folic acid per day is recommended, as the benefits of taking more (which may include masking a diagnosis of vitamin B12 deficiency) are not fully understood. The likelihood of subsequent pregnancies is higher for women who have already had an NTD.

PHENYTOIN (hydantoin, Dilantin)

A medicine called phenytoin is charity to delicacy epilepsy. There is a slight risk of fetal hydantoin syndrome (a group of birth abnormalities) if the mother uses this medicine during the first trimester of pregnancy. Slow growth or marked mental retardation, deformities in craniofacial features and hypoplasia of the distal phalanges are the defect pattern. The major birth defects due to phenytoin are associated with the inability of lymphocytes to of Hydantoin syndrome do not always appear at the same time in twins. The risk of developmental abnormalities in children exposed to phenytoin is between 1% and 11%. The maximum risk from long-term exposure is 10% for all disease and 30% for abnormal ones.

MEDICATIONS

Some over-the-counter (OTC) and prescription drugs are considered teratogenic. Therefore, it is very important to inform your doctor about all the medications you use. Read labels before taking over-the-counter medications or supplements. If you have any questions regarding the safety of the product, contact your doctor. It is best not to use the medicine until you get back from them.

Examples of teratogenic drugs:

Anti-epileptic drugs (AEDs).

Antibiotics.

Anticoagulants (blood thinners).

Antithyroid drugs.

Vitamin A (found in skin care products).

Hormonal drugs.

Health professionals weigh the pros and cons of prescription drugs to determine which drugs are less likely to affect fertility. For example, phenytoin is a drug used to treat epilepsy. It is harmful to the fetus but may be beneficial to pregnant women.

CONCLUSION

Teratogenic effects of drugs during pregnancy are an important problem that doctors and pregnant women should pay attention to. The risks and benefits of drug use during pregnancy should be weighed and, if possible, exposure to teratogens should be avoided during the critical period of fetal development.

Consult your doctor before taking medication during pregnancy. Patients should be educated about non-pharmacological ways to manage stress, pain, and infection during pregnancy. The risk-benefit ratio must justify the use of the drug and the minimum dose should be used.

Patients should be educated about the risks of drug use in society. Caution should be exercised when using the drug during pregnancy, as the long-term effects of the drug in the uterus may take years to appear.

REFFERENCES

1. Henkel L, Willert HE. Dysmelia: a classification and pattern of malformation in a group of congenital defects of the limbs. J Bone Joint Surg 1969;51B:399.

2. McCredie J. Embryonic neuropathy: a hypothesis of neural crest injury as the pathogenesis of congenital malformations. Med J Aust 1974;1:159–163

3. McCredie JM. Comments on ―Proposed mechanisms of action in thalidomide embryopathy. ǁ Teratology 1990;41:239–242.

4. McCredie J, North K, de Iongh R. Thalidomide deformities and their nerve supply. J Anat 1984;139:397–410

5. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. PNAS USA 1994;91:4082–4085

6. Friedman JM. Effects of drugs and other chemicals on fetal growth. Growth Genet 1992;8:1–5

7. Cregler LL, Mark H. Medical complications of cocaine abuse. NEJM 1986;315:149

8. Hodach RJ, Hodach AE, Fallon JE, Folts JD, Bruyere HJ, Gilbert EF. The role of betaadrenergic activity in the production of cardiac and aortic arch anomalies in the chick embryo. Teratology 1975;12:33–45

9. Little BB. Cocaine Abuse during pregnancy: maternal and fetal implications. Obstet Gynecol 1989;73:157–160.

10. Volpe JJ. Mechanisms of disease: effect of cocaine use on the fetus. NEJM 1992;327:399–407

11. Herman GE. Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. Hum Mol Genet 2003;12: 75–88

12. Kelley RI. Inborn errors of cholesterol biosynthesis. Adv Pediatr 2000;47:1–52.

13. Porter FD. Human malformation syndromes due to inborn errors of cholesterol synthesis. CurrOpinPediatr 2003;15:607–613

14. Hayes A, Gilbert A, Lopez G, Miller WA. Mevacor: a new teratogen? Am J Hum Genet 1995;57(suppl 4):A92

15. Thalidomide Teratogenic Effects Linked to Degradation of SALL4: After 60 years, researchers have now shed light on the mechanism underlying thalidomide's devastating teratogenic effects. Am J Med Genet A. 2018 Dec;176(12):2538-2539.

16. Thalidomide: Lenz W. Teratogenicity of Thalidomide: A Reassessment. Proc R Soc Med. 1962 Nov;55(11):943-6. PMID: 13960254

17. Warfarin: Kaur S, Gupta M, Mahajan S, Sodhi JS. Warfarin Embryopathy. Stat Pearls Publishing; 2021.

18. Kumar SP. Fetal alcohol syndrome, mechanisms of teratogenesis. Ann Clin Lab Sci 1982;12:254–257

19. Jones KL. Smith's Recognizable Patterns of Human Malformations, 6th ed, Elsevier Saunders, Philadelphia, 2006; pp 491–494

20. CDC. Fetal alcohol syndrome: Alaska, Arizona, Colorado, New York, 1995–1997. Morb Mortal Wkly Rep 2002;51:433–435

21. Shepard TH. Catalog of Teratogenic Agents, 7th ed, John Hopkins Univ Press, Baltimore, 1992; pp 156–160.

22. Streissguth AP, Landesman-Dwyer S, Martin JC, Smith DW. Teratogenic effects of alcohol in humans and laboratory animals. Science 1980;290:353.

23. Van Allen M, Jilek-Aall L, Rwiza HT. Possible fetal chloroquine syndrome. Proc Greenwood Genet Ctr 1995;14:15

24. Landesman-Dwyer S, Landesman-Dwyer IE. Smoking during pregnancy. Teratology 1979;19:119–125.

25. Naeye RL. Environmental influences on the embryo and early fetus. In: Disorders of the Placenta, Fetus and Neonate: Diagnosis and Clinical Significance (Naeye RL, Ed), Mosby-Year Book, St. Louis, 1989; pp 77–89.

26. Bureau MA, Monette J, Shapcott D, Pare C, Mathieu JL, Lippe J, Blovin D, Berthiaume Y , Begin R. Carboxyhemoglobin concentration in fetal cord blood and in blood of mothers who smoked during labor. Pediatrics 1982;69:371–373.

27. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. PlastReconstr Surg 2000;105:485–491

28. Meyer KA, Williams P, Hernandez-Diaz S, Chattinquis S. Smoking and the risk of oral clefts: exploring the impact of study designs. Epidemiology 2004:15:671–678.

29. Idanpaan-Heikkila J, Fritchie GE, Englert LF, Ho BT, McIsaac WM. Placental transfer of tritiated-1-tetrahydrocannabinol. NEJM 1969;281:330

30. Klausner HA, Dingell JV. The metabolism and excretion of delta-9-tetrahydocannabinol in the rat. Life Sci 1971;10:49–59

31. Kreuz DS, Axelrod J. Delta-9-tetrahydrocannabinol: localization in body fat. Science 1973;179:391.

32. Zellweger H, McDonald IS, Abbo G. Is lysergic-acid-diethyl-amide a teratogen? Lancet 1967;2:1066–1068

33. Golbus MS. Teratology for the obstetrician: current status, ObstetGynecol 1980;55:269–277.

34. Irwin S, Egozcue J. Chromosomal abnormalities in leukocytes from LSD-25 users. Science 1967;157:313–314.

35. Hungerford DA, Taylor KM, Shagass C. Cytogenic effects of LSD-25 therapy in man. JAMA 1968;206:2287–2291.