ISSN No:-2456-2165

Teratogenic Effect of Different Drugs at Different Stages in Pregnancy

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Abstract:- Because of the potential for teratogenic medication effects on the foetus, treating common ailments during pregnancy is challenging. The first eight weeks of human development are referred to as the embryogenesis period, sometimes known as the organogenesis period. Such a deficiency is caused by a teratogenic agent, which are compounds that could harm the human embryo or foetus physically or functionally. An acknowledgment of the tragedies caused by the thalidomide epidemic in the 1970s and the rubella epidemic in the early 1960s in the field of teratology. Chloramphenicol, Warfarin, Valproate, and Thalidomide are a few of the medications that might cause abnormalities such microcephaly, hydrocephalus, spina bifida, and a number of other syndromes. Many of these substances can enter human tissue and a developing foetus, which can have detrimental effects on the human reproductive health. Numerous biological and physical elements, like as radiation and infection, contribute to teratogenic effects.

Keywords:- *Teratogenic, Teratogenicity, Birth Defects, Pregnancy, Early Pregnancy, Miscarriage, Stillbirth, Preterm Birth, Congenital abnormalities.*

I. INRODUCTION

Due to the risk of teratogenic consequences from the drug and physiologic changes in the mother as a result of the pregnancy, drug therapy presents a specific concern during pregnancy [1,7]. When a sperm enters an egg, pregnancy happens. This process, known as fertilisation, often takes place in the fallopian tube of the female. The fertilised egg starts to divide right away, creating a huge mass of cells. The fertilised egg implants into the uterine wall between 5-7 days after ovulation and begins to create the placenta [2]. The first eight weeks of pregnancy are primarily when medications have an impact on how the human embryo develops. The blastocyst is free to move around in the uterus for the first week and relies on uterine secretion for sustenance. At this point, it is unknown if exogenous factors like medications can result in congenital abnormalities, but they can cause the embryo's death [3]. A, B, C, D, or X risk categories were created by the FDA to indicate a drug's potential to cause birth defects if used during pregnancy in 1979 [5]. The formation of deformities in the foetus is referred to as teratogenic. A teratogenic drug causes such a defect. The term "teratogen" is typically used to describe chemicals that impede the normal anatomical development of an embryo [4].

II. STAGES OF PREGNANCY

- *First trimester: - 1 to 3 Months (week1 through 12)*

The first trimester lasts 12 weeks and starts at fertilisation. Pregnancy usually goes like way for the first three months. During this trimester, the fertilised egg will grow from a small group of cells into a foetus that is beginning to exhibit human characteristics [3]. Although the first trimester is delightful, the majority of people also go through this time with painful symptoms including fatigue and morning sickness [5].

- *Second trimester: - 4 to 7 Months (weeks13 through 28)*

The second trimester of pregnancy is usually viewed as the best part. By this time, any morning sickness should have passed, along with any discomfort from the early stages of pregnancy. You may also start to feel movement when the foetus flips and spins inside your uterus. [1].

- *Third trimester: - 8 to 10 Months (weeks29 through 40)*

The last stage of your pregnancy is this. Avoid the temptation to start counting down the days until your due date in the hopes that it will arrive early by resisting the urge. With each week of this final period of development, the foetus prepares for birth. During the third trimester, the foetus gains weight quickly and gains body fat that will be advantageous after birth [6].

III. RISK OF TERATOGENICITY OF DRUGS USED IN PREGNANCY

- *Antiepileptic drugs:*

AEDs have been suspected as having teratogenic potential since the 1960s. Most WWE cannot afford to stop using AEDs because seizures pose a risk of harm or perhaps death [10]. Anti-epileptic medications increase the likelihood of conceiving a kid with congenital abnormalities more than the general population [3]. AED use during the first trimester of pregnancy may increase the likelihood that children delivered to WWE (Well Women Exam) women will require medical countermeasures [10].

- *Analgesics and Anti-inflammatory Drugs:*

Acetaminophen and Propoxyphene are reasonable choice when symptomatic relief of pain is required. Acetylsalicylic acid has probably more widely used in pregnancy but high doses may cause intrauterine growth retardation. Propoxyphene has not been associated with teratogenic effects, but codeine has been related to congenital abnormalities in the respiratory system [3].

➢ *Antidepressants and Anxiolytics Drugs:*

Clinical experience has shown that pregnant women exposed to antidepressants experience greater spontaneous abortions and stillbirths. Poor Neonatal Adaptation (PNA) is more common when pregnant women receive treatment in the third trimester [11]. Diazepam (Valium) use during pregnancy has been linked in certain studies to birth malformations include cleft lip, heart issues, and pyloric stenosis [3]. Due to the possibility of congenital malformations, lithium should be avoided during pregnancy [3].

➢ *Ciprofloxacin and Levofloxacin:*

Levofloxacin and Cipro are examples of other antibiotics. These medications may impair the baby's skeletal and muscular development as well as the mother's joints and possibly even cause nerve damage [21].

IV. HOW DO DRUGS CROSS THE PLACENTA

- Most drugs can cross the placenta by passive diffusion
- Placental membrane is semi-permeable
- Movement of drugs through the placenta is limited by a single layer of trophoblast [31].

V. TERATOGENESIS AND FDA CLASSIFICATION DRUG

➢ *Teratogenesis*

Congenital abnormalities of the foetus occur. These are compounds that, when exposed to an embryo or foetus, can poison them and result in lifelong birth abnormalities. (Mistakes in functionality or structure) [31].

Table 1 FDA Classification Drugs

Category	Characteristics	Examples
A	The foetus in the first trimester of pregnancy is not at risk, according to adequate and controlled research conducted in women.	**Folic acid Thyroxine**
B	There are no controlled trials in pregnant women, despite animal reproductive research failing to show a risk to the foetus	**Paracetamol Erythromycin**
C	Only if the potential benefits outweigh the potential risks to the foetus should drugs be given, regardless of whether studies in animals have demonstrated a harmful effect on the foetus (teratogenic, embryocidal, or other).	**Morphine**
D	Based on data from studies on adverse reactions, there is strong evidence that there is a danger to the human foetus, although the benefits of using the medicine while pregnant may outweigh the risks.	**Antiepileptics**
X	Proven foetal abnormalities in animal and human studies. Drugs should only be administered if the possible advantages outweigh the potential hazards to the foetus [2].	**Thalidomide Sedative**

VI. TERATOGENESIS OF DRUGS AT STAGES

Table 2 First Trimester

FIRST TRIMESTER	
Thalidomide	▪ Phocomelia: - Absence of organ, one or more limbs and is denoted a terminal transverse defect. ▪ Shortened or absent long bones of the limbs
Phenytoin	▪ Foetal Hydantoin Syndrome ▪ Nail and digital hypoplasia ▪ Oral cleft (cleft lip and palate)
Alcohol	▪ Foetal Alcohol Syndrome ▪ CVS abnormalities ▪ CNS abnormalities
Tetracycline	▪ Permanent teeth staining ▪ Discoloration and hypoplasia ▪ Caries and pigmentation of permanent teeth
Corticosteroids	▪ Cleft lip and palate

Warfarin	▪ Hypoplasia of nasal bridge ▪ CNS malformation ▪ Anticoagulant

Table 3 The Second and Third Trimester

THE SECOND AND THIRD TRIMESTER	
Chloramphenicol	▪ Gray baby syndrome
Propranolol	▪ Bradycardia ▪ Neonatal hypoglycaemia ▪ Poor uterine blood flow
NSAIDs	▪ Prostaglandin synthesis inhibitors ▪ Increase risk for postpartum haemorrhage
ACE inhibitor	▪ Renal damage
Antithyroids	Risk for neonatal hypothyroidism and goitres (Methimazole, Carbimazole, Iodide and Propylthiouracil)
Chloramphenicol	▪ Gray baby syndrome

VII. CONCLUSION

The study's analysis of this literature demonstrates that worries about medication use during pregnancy are not limited to the possibility of delivering a kid with a congenital birth defect. Despite the fact that pregnant women exaggerate the teratogenic risk of medicine usage, the majority of the drugs were thought to carry relatively modest risks and substantial rewards. This can be considered by medical professionals when counselling expectant ladies. From the literature, we isolated six key teratogenic pathways related to the use of medical drugs. Numerous other prescription and over-the-counter medications may also promote tumorigenesis through these mechanisms, in addition to the fact that nearly all medicinal pharmaceuticals recognised by Schwarz et al. (2007) as U.S. FDA class X are associated to at least one of these processes. some prescription drugs

REFERENCES

[1]. Patel BG, Patel BK, and Sachdeva P. Consider this: Pregnancy and drug use. 2009 Jan;71(1):1–7. doi: 10.4103/0250-474X.51941. Indian J Pharm Sci. PMCID: PMC2810038; PMID: 20177448.
[2]. Foundation. NHS Options (online) Mother and Child Glossary of the United Nations; [updated on July 9, 2002]. Accessible at: www.hon.ch/Dossier/MotherChild
[3]. Ruedy J. Early-pregnancy drug usage teratogenic risk. 1984 Oct;30:2133-6 in Canadian Family Physician. PMCID: PMC2154342; PMID: 21279129.
[4]. Bonati M., Sharabi S., and Addis A. Are systems that categorise the risks of drug use during pregnancy a credible source of information? Drug Safe, September 2000;23(3):245-53. PMID: 11005706; doi: 10.2165/00002018-200023030-00006.
[5]. Drugs.com: New FDA Pregnancy Categories Described
[6]. Week-by-week Stages of Pregnancy: Foetal Development
[7]. https://my.clevelandclinic.org/health/articles/7247-fetal-development-stages-of-growth
[8]. Evans JM, Libby G, Crombie IK, Flynn RW, and Irvine. Prenatal medication prescribed in primary care: a record-linkage study in Tayside, Scotland. safe for drugs. PMID: 20553060. 2010 Jul 1;33(7):593-604. doi: 10.2165/11532330-000000000-00000.
[9]. Ridley E., Alván G., Prame B., Kihlström I., Sannerstedt R., Lindborg P., Danielson BR. Prescriber education and risk classification for medications during pregnancy. safe for drugs. doi: 10.2165/00002018-199614020-00001. PMID: 8852521. 1996 Feb;14(2):69-77.
[10]. Meador KJ and Gedzelman E. Anti-epileptic medications for pregnant women with epilepsy. The Advance. safe for drugs. 2012 Apr;3(2):71-87. doi: 10.1177/2042098611433192; PMCID: PMC4110845; PMID: 25083227.
[11]. Bogy E., Belovicova K., Csatlosova K., and Vicky M. risks associated with SSRI and SNRI antidepressant use during lactation and pregnancy. Multidisciplinary Toxicology. 10.1515/intox-2017-0004. PMID: 30123033; PMCID: PMC6096863. 2017 Sep;10(1):30–34.
[12]. Safety of Drugs Taken During Pregnancy. Jin J. JAMA 2022;328(5):486;10.1001/jama.2022.8974
[13]. Human Reproduction Update 16(4):378–94 (January 2010) Medications' teratogenic mechanisms.
[14]. An international cooperative study on medication during pregnancy. C.G.D.U.P. (Collaborative Group on Drug Use in Pregnancy). PMID: 1360913 Int J Gynecol Obstet 1992 Nov;39(3):185-96.
[15]. Oakley GP Jr. human congenital deformities' frequency. PMID: 2945687. Clin Perinatol. 1986 Sep;13(3):545-54.
[16]. Holmes AP, Burkey BW. What every chemist should understand about evaluating pharmaceutical use during pregnancy and breastfeeding. 2013 July;18(3):247-58 in J Pediatr Pharmacology Ther. doi: 10.5863/1551-6776-18.3.247. PMCID: PMC3775560; PMID: 24052789.

[17]. Lo WY and JM Friedman. Recent drug introductions' teratogenic potential in human pregnancy. 2002;100(3):465-473 in Obstet Gynecol. [PubMed] Using Google Scholar
[18]. Damaged G and Pernia S. The new labelling rule for pregnancy and lactation. P T. 2016 Nov;41(11):713-715. PMCID: PMC5083079. PMID: 27904304.
[19]. Berukhim, K., Abrouk, M., and Farahnik, B. Effects of the Pregnancy and Lactation Labelling Rule (PLLR) on dermatologists in practise. 2015;21(11) pii: 13030/qt46c4m2tw. Dermatol Online J. [PubMed] Using Google Scholar.
[20]. Food and Drug Administration (20). The FDA publishes a final regulation about updates to the information on prescription drugs and biological products regarding pregnancy and breastfeeding. Dec 3, 2014. (Retrieved on February 13, 2016). Available at: ucm425317.htm at www.fda.gov/NewsEvents/Newsroom.PressAnnouncements.
[21]. The following medications should be avoided when pregnant, according to Zara Risoldi Cochrane, Pharm.D., M.S., FASCP. — Published on May 7, 2019 by Chaunie Bruise
[22]. Poonam Sachdeva Department of Pharmacology, A. R. College of Pharmacy, Vallabh Vidyanagar-388 120, India, on the subject of drug use during pregnancy.
[23]. Risk and benefits of drug usage during pregnancy: Banhidy F, Lowry RB, Czeizel AE. Int J Med Sci 2005;2:100–6.
[24]. Melton MW: Should I take two aspirin? the dangers of taking medications while pregnant. 1999; 4:25–32 in Mother Baby J.
[25]. Ward RW. challenges in researching the harmful consequences of prenatal medication therapy on the foetus and the newborn. 2001; Semen Perinatol 25:191–5.
[26]. Loebstein R, Larkin A, and Korean G. Pregnancy-related pharmacokinetic alterations and their clinical significance. 33:328–43 Cline Pharmacokinetic, 1997.
[27]. Lewes L. Which medications are safe in pregnancy? Patient Care 2000;34:19
[28]. Meadows M. Pregnancy and the drug dilemma. FDA Consumer Magazine 2001.
[29]. De Jong LT, Van den Berg PB. A study of drug utilization during pregnancy in the light of known risks. Int J Risk Safety Med 1990;1:91-105.
[30]. Yaffe SJ, editor. Drugs in pregnancy and lactation. 6th ed. Philadelphia: Lippincott William Wilkins; 2002
[31]. L5- Teratogens and Drugs of Abuse in Pregnancy, Pharmacology team 438.
[32]. Jessica C. Leek; Hasan Arif. Pregnancy Medication. Updated 2022 Jul 25. In: Stat Pearls Internet.
[33]. Verstegen RHJ, Ito S. Drugs in lactation. J Obstet Gynaecol Res. 2019 Mar;45(3):522-531. [PubMed]
[34]. U.S. Department of Health & Human Services. FDA Pregnancy Categories. *(https://chemm.hhs.gov/pregnancycategories.htm)* Accessed 10/21/2022.
[35]. 35. The March of Dimes. pregnancy and drug use. (https://www.marchofdimes.org/pregnancy/street-drugs-and-pregnancy.aspx) on October 21, 2022.
[36]. Lo WY, Friedman JM, number 36. Recent drug introductions' teratogenic potential in human pregnancy. 2002;100(3):465-473 in Obstet Gynecol. [PubMed] Using Google Scholar
[37]. Nelson MM and Forfar JO drug use during pregnancy and the risk of a foetus having congenital defects. BMJ, 1971 Mar 6, 1(5748), 523-527. [Free PMC article] [Google Scholar] [PubMed]
[38]. DRUGS AND THE EMBRYO, by Wheatley D. Br Med J, 1(5383), 630, 1964 Mar 7. [Free PMC article] [PubMed] Using Google Scholar
[39]. Bracken MB, Helford TR Prescription drug use during pregnancy and the risk of congenital defects. Obstet Gynecol, September 1981, 58(3):336-44. PMID: 7266953.
[40]. T1 - Teratogenicity: A brief summary of typical teratogenic substances based on a mechanism Asian Pacific Journal of Tropical Disease 4(6):421-432 December 2014.
[41]. Appolinary Kamuhabwa and Rashida Jalal Dng uSe in pregnancy: Knowledge of drug dispensers andpregnant women in Dar as Salaam, Tanzania2011 May-Jun
[42]. Punam Sachdeva," B. G. Patel, and B. K Patel' Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb
[43]. Brittney D Bastow, MD; Chief Editor: Christine Isaacs, MD Teratology and Drug Use during Pregnancy Nov09, 2022
[44]. Raul Artal-Mittelmark , MD Slags of Development of the Foetus May 2021
[45]. S. Raul Artal-Mittelmark , MD Stages of Development of the Fetus May 2021
[46]. Lorenzo Crumbie MBBS, BSc Embryology: 2nd week of development July 19, 2022
[47]. Larissa Hirsch, MD Female Reproductive System June 2019 JETIR2212018 | Journal of Emerging Technologies and Innovative Research (JETIR) www.ietir.orga159www.jetir.org (ISSN-2349-5162)
[48]. Raul Artal-Mittelmark , MD Stages ofDevelopment of the Fetus May 2021
[49]. Australas J UItrasound Med. The development, structure and blood flow within the umbilical cord withparticular reference to the venous system
[50]. Tan C.M.J. . Lewandowski A.J. the Transitional Heart: From Early Embryonic and Fetal Development