A CONCISE OVERVIEW ON TERATOGENIC DRUGS

Arya Mudgal\*, Payal Rani Chaudhary, Yogesh Joshi

Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun-248001, Uttarakhand, India.

**\*Corresponding Author: aryamudgal055@gmail.com**

**ABSTRACT**

A small percentage of documented congenital malformations with a recognised aetiology, about 1%, are problems related to pharmacological therapy. This shows that responsible and cautious drug use is a viable way of prevention among fertile women, especially pregnant women.It takes careful consideration of both experimental data from animals and human experience to identify a drug's teratogenic effect. 40% of pregnancies are unplanned, therefore it stands to reason that any medication with teratogenic potential should only be administered under close medical supervision. Also, adequate awareness of a drug's potential teratogenicity allows for modification of treatment prior to conception. Any medication should only be used if absolutely essential during pregnancy, therefore it is recommended that only those with adequate information and past clinical expertise be used. When there is any question, Teratology Information Services can help both medical professionals and patients.

**PURPOSE OF THE STUDY**

The purpose of this article is to explore the potential teratogenic effects of various drugs on fetal development during pregnancy. It aims to provide a comprehensive overview of different drug categories and their associated risks to pregnant women and their unborn babies. The article emphasizes the importance of responsible and cautious drug use among fertile and pregnant women to prevent congenital malformations. It discusses the significance of understanding drug classifications and their implications for pregnancy, as well as the need for regular updates to these classifications based on the latest research. The article also delves into specific drug categories, such as antibiotics, benzodiazepines, hormones, and others, detailing their potential impact on fetal development and highlighting the importance of informed decision-making when considering their use during pregnancy. It underscores the necessity of medical supervision, careful consideration, and proper counseling for pregnant women regarding drug usage, especially in cases where unintended exposure may have occurred during the early stages of pregnancy

**Keywords** - Pregnant, Drugs, Teratogenic, Medication, Women, Harmful

**I. INTRODUCTION**

Congenital defects, which might be related to structural, anatomical, metabolic, or functional problems, may occur in 5% of all births (including mental retardation). Genetic aberrations, physical, viral, or chemical factors are possible causes, which respond throughout foetal life, causing persistent harm to the subject's health and necessitating medical care [1,2]. Genetic factors are the likely culprit in 25% of cases, whereas environmental (chemical, physical, or biological) variables are the likely culprit in 10% of cases and can directly affect and alter embryo-foetal development [3].

Around 1% of all congenital abnormalities with established aetiologies are caused by exogenous factors, including medicines [4]. As a result, safe and responsible drug use is an important component of effective and attainable prevention in fertile or pregnant women.

In clinical practise, numerous pharmacological risk classifications for pregnancy that have been assembled by different countries might be referred to. In specifically, the American Food and Drug Administration (FDA) developed five pharmacological classifications in 1979 based on information gathered from both human and animal subjects: A, B, C, D, and X

* Category A: There is no indication of a risk to the foetus during the first trimester of pregnancy in controlled trials in men, and there is little chance that the foetus would suffer harm.
* Category B: There are no controlled human trials; reproductive research in animals have not shown a harm to the foetus. or research involving animals point to a damaging outcome (other than a decline in fertility) that hasn't been proven by careful study in pregnant individuals. (Nevertheless, there is no proof that damage occurred during the later stages of pregnancy.)
* Category C: No controlled trials have been conducted in women, or there are no studies available in either men or animals, despite research in animals showing deleterious (teratogenic, lethal, or other) effects on the foetus. Only if the potential benefit outweighs any potential risk to the foetus should the medication be provided.
* Category D: There is proof of a danger to the foetus in males, although there may be benefits to using the drug during pregnancy that outweigh the danger (e.g., the medication is required for the patient's survival or to treat a serious condition when safer medications are unavailable or ineffective.
* Category X:There is evidence of harm to foetuses based on personal experience or research on animals and people that has identified foetal abnormalities, or both, and using the substance while pregnant definitely carries more risk than reward. Pregnant or potentially pregnant women should not take the medication.

Pregnant women are advised to avoid drugs in class A, while class X drugs have a history of teratogenicity. These classifications are usually incomplete and out of date in practise, which makes it challenging for doctors to interpret them and causes patients' concern. If the classifications are to be a useful starting point for assessing pharmaceutical risk, they must be revised on a regular basis to include the most recent data from the literature as well as a thorough clinical examination of each patient[5].

**TABLE A: Adverse effects of some due to teratogenic drugs**

|  |  |
| --- | --- |
| **Category** | **Effects** |
| Antibiotic (tetracycline) | Discoloured teeth, Bone effects |
| Benzodiazepines | Hypotonia , Apnoea |
| Diethylstilbestrol | Vaginal carcinoma |
| NSAIDS (aspirin) | Oligohydramnios , Precocious botallo’s duct closure |
| Iodine | Hypothyroidism |
| Lithium | Ebstein anomaly , Cardiac failure , Flotpy new born syndrome |
| Hormones (endrogen) | Virilization , Esophageal , Cardiac defects |
| Vitamin A | Spina Bifida |
| Thalidomide | Phocomelia , Beafness , Mental redardation |

**II. TERATOGENIC DRUGS**

1. **Antibiotics:** Aminoglycosides have been linked to hearing function deficits in foetuses. Particularly for streptomycin and kanamycin, this impact has been shown [6,7].Tetracyclines are prohibited during the second and third trimesters due to their ability to change a person's normal dentition and to create bone deposits during the growing process. These antibiotics induce yellowish-brown or greyish-brown discoloration of the teeth., depending on the dosage and duration of exposure.They can also slow bone formation in 40% of instances, mostly in the fibula [8,9].Moreover, intravenous tetracycline treatment might cause liver necrosis[10].At times of pregnancy, penicillin and its variants are the antibiotics of choice. Cephalosporins and macrolides are possible substitutes.
2. **Benzodiazepines:** While using benzodiazepines in the weeks leading up to birth may increase the risk of labiopalatoschisis, They can also cause apnea, hypotonia, hypothermia, and newborn abstinence syndrome with signs and symptoms of neuromuscular excitability. When the clinical circumstances of the patient warrant the use of benzodiazepines during pregnancy, It is better to use those with the shortest half-lives and divide them into two or more daily doses. Additionally, if they were suspended at least two weeks prior to birth, that would be great. [11-13].
3. **Diethylstilbestrol:** According to a number of studies [14–15], intra-uterine exposure to diethylstilbestrol may increase the risk of developing vaginal or uterine cervix clear cell adenocarcinoma. At least 25% of women who were born with abnormalities of the reproductive system, Vaginal adenosis, cervical, vaginal, and uterine septa abnormalities, and tubaric deformities are examples of such conditions, During their moms' first trimester of pregnancy, they were exposed to this synthetic oestrogen. [16,17]. The male reproductive system has also displayed anomalies in the sons of women who were exposed to this medication while pregnant [18].
4. **Non-steroidal anti-inflammatory drugs (NSAIDs):** In the second and third trimesters, the use of NSAIDs is associated with oligohydramnios, anuria, and, close to term, precocious Botallo's duct closure, which can cause pulmonary hypertension, cerebral hemorrhage, and necrotizing enterocolitis (NEC) [19–20]. Paracetamol is the medicine of choice for analgesic, anti-inflammatory, and antipyretic effects during pregnancy.
5. **Iodides and Iodine:**Increased iodide exposure during pregnancy, which could happen in circumstances of long-term usage of particular Even in their most severe forms, expectorants and topical disinfectants can cause goitre and hypothyroidism in newborns [21-22]. Only starting in the tenth week of pregnancy is it feasible to harm the developing thyroid. Due to the thyroid's inability to absorb iodine, exposure before the tenth week need not be regarded as hazardous[29]. Eight days is the half-life of iodine, which is utilised in both medicinal and diagnostic treatments. Because the doses often employed in diagnostic procedures would expose embryos to radiation at considerably lower levels than those deemed harmful, it is unlikely that they might cause radiation damage. However, therapeutic levels may increase the risk of miscarriage, foetal deformities, thyroidal ablation, mental retardation, neoplasm, and, most significantly, leukaemia [23-24].
6. **Lithium:** Lithium use during pregnancy is linked to an increased risk of cardiovascular abnormalities, especially the Ebstein anomaly. The risk is between 10 and 20. compared to the general population, times higher. Such a danger, which rests at values less than 1% [25,26], is in any event lower than that which was initially indicated by several authors. Additional potential Neonatal goitre, diabetes insipidus, cardiac arrhythmia, congestive cardiac failure, and floppy newborn syndrome are all problems. [27,28].When using lithium while pregnant, it's crucial to keep the dosage as low as possible while managing lithaemia once a month throughout the first half of the pregnancy and once a week thereafter that until delivery.It may be possible to try replacing lithium with another antipsychotic medication or a tricyclic antidepressant in some carefully chosen patients and when preparing for a potential pregnancy [2].
7. **Androgen-stimulating hormones:** Use of androgenic hormones while the female foetus's external genitalia are developing (8th–10th week may result in varying degrees of virilization It goes without saying that the risk is dose and time dependant and cannot be quantified. Even during the crucial stage of embryo development, the progestin dosage in the majority of anticonception drugs makes it difficult to detect an androgenic impact. [29-31].
8. **Vitamin A in high doses:** Vitamin A teratogenicity has long been a source of contention. Until 1986, the FDA had received reports of around 18 cases of teratogenic effects caused by high doses of vitamin A (18,000-150,000 IU/diem), with a pattern similar to that of retinoids. [32,33]. These findings contrast with the findings of a collaborative investigation of 312 newborns who were not teratogenic but were born to women who had taken large doses of vitamin A (median 1/4 50,000 IU/diem) [34]. Because the potential teratogenic effect of vitamin A is still unknown, the American Society of Teratology advises women of reproductive age not to exceed 8000 IU/diem [35].
9. **Thalidomide:** The model for teratogens is thalidomide. Since 1950, it has been used to treat insomnia; nevertheless, in the 1960s, occurrences of limb deformities occurred newborns individuals were given the drug throughout the first trimester. It has been estimated that 8000 or so infants worldwide have been born with abnormalities as a result of thalidomide. The main birth defects brought on by this medicine Phocomelia, amelia, heart difficulties, renal and gastrointestinal malformations, deafness, microtia, anotia, mental retardation, and autism are examples of these conditions. A 20% rise in the incidence of teratogenicity occurs between days 34 and 50 of pregnancy [36,37]. A prospective AIDS medication, TB, Behcet's syndrome, leprosy, and other conditions illnesses is being investigated at the moment: thalidomide. The FDA approved thalidomide in 1998 for the treatment of cutaneous leprosy. Following this, reports of 33 further cases of thalidomide-induced embryopathy were sent to Brazil. To educate the public about thalidomide, the System for Thalidomide Education and Prescribing Safety (STEPS) campaign was formed. [38,39].

**III. Clinical significance**

To avoid any negative effects on the mother and the foetus, physicians must give the pharmaceutical management of pregnant women special thought and close collaboration. Clinicians should be extremely cautious when prescribing any prescription to pregnant women and be aware of the most recent information regarding drug safety during pregnancy in light of the terrible side effects of thalidomide[39].

**IV. CONCLUSION**

In reality, few medications are clearly teratogenic in people, and there aren't many congenital problems that can be linked to them. An efficient preventive measure for these problems is therefore possible because the drugs in question are well recognised in the medical community and every woman of reproductive age who uses them is duly told of the potential risks. In one of the study 40% of births are unanticipated, it is critical that these medications be administered under the guidance of a physician and by professional prescription, preventing any chance of self-medication in any way. The length of any potential waiting period before conception should be made explicit when appropriate. In any case, using potentially teratogenic pharmaceutical treatments is not prohibited during pregnancy so long as they are used while the foetus is not susceptible to them. Only situations when a medicine has been shown to be necessary and effective should be administered during pregnancy.Additionally, since every new medicine has a risk of being teratogenic, it is advisable to utilise drugs for which information is publicly available and previous clinical experience is easily accessible.It is recommended for women who unintentionally consumed medications during the first trimester of their pregnancy to contact the Teratology Information Services. These services give personnel with expertise in reproductive risk factors who are able to evaluate any risk both qualitatively and quantitatively and offer adviceon the most appropriate diagnostic research when necessary.Each and every pregnant drug counselling facilityhas found that unintentional medication usage during the first trimester has a significant psychological impact on the expectant mother. The drug's instruction pamphlet or the woman's doctor provide her with the most of the information; some of it is incredibly broad or downright alarming, which can sometimes lead to the woman being persuaded to abort the pregnancy. It is essential that these women are informed completely and truthfully about any dangers associated with the relevant medication, to the best of our current scientific understanding. It is inaccurate to generalise about teratogenic effects. This must be qualified and quantified within reasonable bounds in relation to the type of exposure, the stage of pregnancy, and the patient's clinical history, while also taking into account the prevalence of congenital defects in the general population or the presence of additional potential risk factors.

**REFERENCES**

1. Beckam DA, Brent RL. Mechanism of teratogenesis. Annu Rev PharmacolToxicol1984;24:483-500.
2. De Santis M, Carducci B, Cavaliere AF, De Santis L, Straface G, Caruso A. Drug-induced congenital defects. Strategies to reduce the incidence. Drug Safety 2001;24(12):889-901.
3. Shepard TH. Catalog of teratogenic agents. 8th ed. Baltimore: Johns Hopkins University Press; 1995.
4. Koren G. Maternal-fetal toxicology: a clinician’s guide. 2nd ed. New York: Marcel Dekker Inc.; 1994.
5. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 5th ed. Baltimore: Williams and Wilkins; 1998.
6. Robinson GC, Cambon KG. Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. N Engl J Med 1964;271:949–51.
7. Conway N, Birt BD. Streptomycin in pregnancy: effect on the fetal ear. Br Med J 1965;2:260–3.
8. Rendle-Short TJ. Tetracycline in teeth and bone. Lancet 1962;1: 1188.
9. Kutscher AH, Zegarelli EV, Tovell HM, Hochberg B, Hauptman J. Discoloration of deciduous teeth induced by administrations of tetracycline antepartum. Am J ObstetGynecol1966;96:291–2.
10. Allen ES, Brown WE. Hepatic toxicity of tetracycline in pregnancy. Am J ObstetGynecol1966;95:12–8.
11. Saxen I, Saxen L. Associations between maternal intake of diazepam and oral clefts. Lancet 1975;2:498.
12. American Academy of Pediatrics. Committee on Drugs. Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. Pediatrics 2000;105(4 Pt 1):880–7.
13. Laegreid L, Olegard R, Walstrom J, Conradi N. Teratogenic effects of benzodiazepine use during pregnancy. J Pediatr1989;114:126– 31.
14. Robboy SJ, Szyfelbein WM, Goellner JR, et al. Information for physicians. Prenatal diethylstilbestrol (DES) exposure: recommendations of the diethylstilbestrol-adenosis (DESAD) project for the M. De Santis et al. / European Journal of Obstetrics &Gynecology and Reproductive Biology 117 (2004) 10–19 17 identification and management of exposed individuals. NIH Publication 81-2049; 1981.
15. Hatch EE, Palmer JR, Titus-ErnstoffL, et al. Cancer risk in women exposed to diethylstilbestrol in utero. JAMA 1998;280:630–4.
16. Jefferies JA, Robboy SJ, O’Brien PC, et al. Structural anomalies of the cervix and vagina in women enrolled in the diethylstilbestrol adenosis (DESAD) project. Am J ObstetGynecol1984;148:59–66.
17. Palmer JR, Hatch EE. Infertility among women exposed prenatally to diethylstilbestrol. Am J Epidemiol 2000;151:S10.
18. Pal L, Shifren JL, Isaacson KB, et al. Outcome of IVF in DESexposed daughters: experience in the 90s. J Assist Reprod Genet 1997;14:513–7.
19. Levin DL. Morphologic analysis of the pulmonary vascular bed in infants exposed in utero to prostaglandin synthetase inhibitors. J Pediatr1978;92:478–83
20. Major CA, Lewis DF, Harding JA, Porto MA, Garite TJ. Tocolysis with indomethacin increases the incidence of necrotizing enterocolitis in the low-birth-weight neonate. Am J ObstetGynecol1994;170:102–6.
21. Wolff J. Iodide goiter and the pharmacologic effects of excess iodide. Am J Med 1969;47:101–24.
22. Committee on Drugs. American Academy of Pediatrics: Adverse reactions to iodide therapy of asthma and other pulmonary diseases. Pediatrics1982;57:2724
23. Brent RL. Radiation teratogenesis. Teratology 1980;21:281–98.
24. Otake M, Schull WJ. In utero exposure to A-bomb radiation and mental retardation: a reassessment. Br J Radiol1984;57:409–14.
25. Nora JJ, Nora AH, Toews WH. Lithium, Ebstein’s anomaly and other congenital heart defects. Lancet 1974;2:594–5.
26. Kallen B. Comments on teratogen update: lithium. Teratology 1988;38:597.
27. Mizrahi EM, Hobbs JF, Goldsmith DI. Nephrogenic diabetes insipidus in transplacental lithium intoxication. J Pediatr 1979; 94:493–5.
28. Karlsson K, Lindstedt G, Lundberg PA, Selstam U. Transplacental lithium poisoning: reversible inhibition of fetal thyroid. Lancet 1975;1:1295.
29. Castilla EE, Orioli IM. Teratogenicity of misoprostol: data from the Latin-American Collaborative Study of Congenital Malformations (ECLAMC). Am J Med Genet 1994;51:161–2.
30. Hendrickx AG, Korte R, Leuschner F, et al. Embryotoxicity of sex steroid hormone combinations in nonhuman primates. I. Norethisterone acetate ethinyl estradiol and progesterone þ estradiol benzoate (Macaca mulatta, Macaca fascicularis, and Papio cynocephalus). Teratology 1987;35:119–27.
31. Kallen B, Castilla EE, Robert E, Lancaster PAL, Kringeelbach M, Mutchinick O, et al. An international case-control study on hypospadias. The problem with variability and the beauty of diversity. Eur J Epidemiol1992;8:256–63.
32. Monga M. Vitamin A congeners. Semin Perinatol 1997;21(2): 135-42.
33. Rothman KJ, Moore LL, Singer MR, Nguyen U-SDT, Mannino S, Milunsky A. Teratogenicity of high vitamin A intake. N Engl J Med 1995;333:1369–73.
34. Mastroiacovo P, Mazzone T, Addis A, et al. High vitamin A intake in early pregnancy and major malformations: a multicenter prospective controlled study. Teratology 1999;59:7–11.
35. Teratology Society position paper: recommendations for vitamin A use during pregnancy. Teratology 1987;35(2):269–75.
36. Leck IM, Millard ELM. Incidence of malformations since the introduction of thalidomide. BMJ 1962;2:16–20.
37. Stephens TD, Fillmore BJ. Hypothesis: thalidomide embryopathyproposed mechanism of action. Teratology 2000;61:189–95.
38. Zeldis JB, Williams BA, Thomas SD, Elsayed ME. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. Clin Ther 1999;21(2):319–30.
39. Miller MT, Stromland K. Teratogen update: thalidomide: a review. Teratology 1999;60:306-21.