Career Point International Journal of Research(CPIJR)
©2022 CPIJR | Volume 1 | Issue 2 | ISSN : 2583-1895

Teratogenic effect of various drug at different stage of Pregnancy

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Abstract- On the day of fertilisation, when one sperm enters the ovum (egg) and joins with it to form one cell, development begins. Pregnancy lasts for 9 weeks, which are split into three trimesters, and is known as the embryogenesis phase for the first 8 weeks of human development. This period is also referred to as the organogenesis period. Because all medications taken by the female have the potential to have negative effects on the developing foetus or nursing baby, pregnancy and lactation constitute a unique clinical setting where drug therapy raises significant concerns. The first trimester of pregnancy is when medicines can do the most harm.. Around the world, birth abnormalities cause the deaths of almost 3.3 million children under the age of five every year. Teratogenesis is the process of a foetus developing abnormalities. Such a deficiency is caused by a teratogenic agent, which are substances that can cause physical or functional problems in the human embryo or foetus. Following the horrors of the thalidomide pandemic in the 1970s and the rubella epidemic in the early 1960s, interest in the field of teratology sought attention. Drugs including chloramphenicol, warfarin, valproate, and thalidomide can cause anomalies such microcephaly, hydrocephalus, phocomelia, spina bifida, and a number of syndromes. Teratogenicity cannot be treated, but it can be avoided by abstaining from dangerous medicines and taking the necessary safety measures.

Key Words- Teratogens, Teratogenicity, Birth defects, Pregnancy, Thalidomide.

I INTRODUCTION

Teratogenicity is the capacity of a material, organism, or physical agent to alter the course of an embryo's or foetus' development. Birth abnormalities or malformations may result from exposure to teratogenic chemicals, and the degree and kind of consequences depend on the timing of exposure during pregnancy, the dose or duration of exposure, and the individual's genetic predisposition.Teratogenicity describes a substance's or an environment's capacity to affect foetal development abnormally, resulting in congenital abnormalities or birth defects.

Teratogens, which can include drugs, alcohol, viruses, radiation, and environmental contaminants, are those chemicals or elements.

The timing and length of teratogen exposure during pregnancy, as well as the dose and the growing foetus' genetic sensitivity, all affect the outcomes. The most crucial time for foetal development is during the first trimester of pregnancy, and exposure to teratogens then can have the most serious effects.

Teratogenic substances, which can affect foetal growth and development, include numerous medications, chemicals, radiation, viruses, and other environmental elements. The timing, duration, and dosage of exposure as well as the fetus's genetic predisposition are a few of the variables that affect the degree and kind of abnormalities.

For instance, a medication called thalidomide was prescribed to alleviate morning sickness in the early 1960s. There have been reports of phocomelia, a congenital abnormality in which the hands and feet are connected to short arms and legs, as a result of exposure of the foetus during this early period of development. The types or severity of defects brought on by a teratogenic substance also depend on the mother's and fetus's genetic susceptibilities. For instance, the amount of metabolites the foetus is exposed to and how long it is exposed to them will depend on the variance in maternal metabolism of a certain drug. The result will also depend on the foetus' genetic vulnerability to a particular teratogenic chemical.

1.2 DRUGS AND BIRTH DEFECTS

The whole context of developmental abnormalities in humans must be considered when evaluating the clinical effects of pharmacological teratogens. Defects may result from unknown, or genetic origins. 25% of them are known to have genetic (chromosomal, Mendelian, etc.) roots. Though the cause of about 65% of abnormalities is ostensibly unknown, they are likely the result of both genetic and environmental factors (polygenic/multifactorial). The background rate, which for large malformations in the general population is typically quoted as 2-3%, must be contrasted with the risk for deformity after exposure to a medicine. Anencephaly, cleft palate, congenital heart disease, or significant malfunction (such as mental retardation) are examples of serious malformations that are incompatible with survival and require substantial surgery to cure.

Almost any substance that the mother takes while she is pregnant has the potential to harm the foetus and cause an anatomical abnormality (teratogenic). Almost all lipid-soluble substances pass the placenta without any problems. When a substance has a reduced molecular weight, it

can move through water more readily. The amount of a medicine that is free to cross the placenta is also influenced by how much of the drug is bound to plasma protein. With the exception of big organic ions like insulin and heparin (both fractionated and unfractionated), the majority of medications pass the placenta to some extent.

1.3 ARIABLES AFFECTING TERATOGENESIS

Dosage:

Although it is typically true that high doses of a known teratogen are more harmful than low levels, this is not always the case. An embryo may react to a teratogen in one of three ways at any given time: (1) there is no effect at low doses; (2) a pattern of organ-specific malformations may appear at intermediate doses; or (3) the embryo may be killed at high doses, causing the organ-specific teratogenic action to go undetected. Teratogens affect on animals within a relatively small dose range, typically a fourth to a half of the typical dose that would kill the mother. The developmental stage at which the medicine is given also affects the outcome. In other words, a substance can only be teratogenic at a specific dose or stage. Similar to this, an agent may be teratogenic but not lethal at one dose level, while being either lethal or teratogenic at a different one.

1.4 Stage of Embryonic Development:

It is critical to determine when a potential teratogen is introduced to the foetus during development. There are three stages of susceptibility that can be distinguished, with different times for each organ system . (1) During the first few weeks of life, possibly two weeks following conception in humans, the embryo is relatively resistant to teratogenic insults.2 Although a severe injury may kill the embryo, survivors typically show no organ-specific abnormalities. It is assumed that the reason is that early embryonic cells have not irreversibly differentiated. If one cell is destroyed, another one that survives might be able to take over.

(2) Organogenesis, the process of organ differentiation, takes place in the majority of human organ systems between embryonic weeks 3 and 8 (menstrual weeks 5–10); the brain and gonads, however, differentiate later. Susceptibility to teratogens peaks throughout organogenesis. Teratogens have an organ-specific mode of action; they may have an impact on one system of an organ during one stage of development but another system during a different stage. Thus, the precise timing of the damage influences both whether a malformation will develop and the precise range of aberrations.

(3) Following organogenesis, the main feature of embryonic development is an increase in organ size. This time period starts 8 to 10 embryonic weeks before the majority of human organ systems. A teratogen may have an impact on an organ's size or the embryo's general growth during this time. On the other hand, obvious defects are not anticipated. For instance, administration of androgens to a pregnant woman after the 12th week may result in the female fetus's clitoral growth but not the displacement of the urethral opening or the fusion of the labioscrotal folds. In general, a medication that negatively affects a newborn also negatively affects an older foetus. Anomalies can also be the result of side effects.

1.5 Genotype:

There are two well-known genetic pathways that could rationally explain variations in genetic susceptibility: polygenic inheritance and monogenic or Mendelian inheritance. Drug handling variations across people, and subsequently variations in teratogenic vulnerability, are likely to be polygenic in nature. In polygenic inheritance, it is presumable that multiple genes collectively influence a particular feature. Regarding genetic liability, the genotypes cause ongoing variability. When the three stages of drug catabolism are considered—maternal ability to absorb or metabolise a teratogen, placental transfer, and foetal metabolism—this mechanism makes the most sense. Compared to dizygotic twins, adult monozygotic twins handle medications more similarly, yet not identically enough to be explained by a single gene. Monogenic factors do, however, exist.

A single mutant allele in a small number of people may make them either particularly vulnerable to or resistant to certain medications. We refer to these people as having a pharmacogenetic disease. Examples include a lack of pseudocholinesterase, resistance to the blood thinners warfarin and heparin, and the inability to catabolize (decarboxylate) medications like hydralazine or isoniazid. Comparatively, a mutated allele could prevent a foetus from neutralising a possible teratogen. Thus, the administration of a particular teratogen may have negative effects on that foetus but not on other (normal) foetuses.

1.6 Drug Interactions:

When two teratogens are administered simultaneously, the results may differ from when they are administered individually. Folic acid, for instance, inhibits cortisol-induced teratogenesis in mice8, maybe as a result of the stimulation of enzyme systems that break down the teratogen or compete with it for binding sites. On the other hand, one substance might increase the

teratogenic potential of another. For instance, the rat teratogenicity of aspirin is increased by the food preservative benzoic acid. Inhibition of enzymes, the eradication of cells that produce enzymes, and the saturating of binding sites on carrier proteins are potential processes that, if present, would lower concentrations of the unbound active teratogen.

II EFFECTS OF THERAPEUTIC DRUGS:

Thalidomide:

In the 1960s, thalidomide was utilised in clinical settings. It resulted in malformations of the limbs being reduced, facial hemangiomas, oesophagus and duodenal atresia, heart defects (such as tetralogy of Fallot), renal agenesis, urinary tract anomalies, vaginal defects, dental anomalies, ear anomalies, facial palsy, ophthalmoplegia, anophthalmia, microphthalmia, and coloboma. Rare cases of cleft palate did not impact the central nervous system. The kids were averagely intelligent. 23 to 28 days after conception was the sensitive window for the development of human thalidomide birth abnormalities, with 14 days being the key window. Around 20% of pregnancies exposed during this time resulted in newborns with anomalies, the most noticeable of which were limb deformities, often with preaxial polydactyly of six or seven toes per foot and ranging from triphalangeal thumb to tetra Amelia or phocomelia of the upper and lower limbs.

Fig 1: THALIDOMIDE EFFECT

McCredie proposed that the pathogenetic foundation of the limb deformities was interference with neural crest-based sclerotomalorganisation. By attempting to ascertain whether neural crest injury would impair development of structures supplied by the sensory autonomic nerves derived from the injured zone of the neural crest, McCredie and colleagues expanded their

studies of the visceral anomalies in infants who died with multiple congenital anomalies and longitudinal limb defects. When the autopsy data were applied to sclerotomal and viscerotomal maps, 89% of cases had a neuroanatomic link. Based on neurotomes or embryonic developmental fields with shared regional innervation, the authors postulated a developmental link within a multiple congenital abnormality syndrome. Thalidomide inhibits angiogenesis, and its teratogenicity is correlated with its antiangiogenic effect.

III Folic acid deficiency and folic acid antagonists:

Numerous women who have given birth to children with neural tube defects (NTDs) have been shown to have folic acid deficiencies; folic acid antagonists may also cause NTDs. Up to 70% of NTDs, especially anencephaly, seem to be caused by folic acid deficiency. The US Food and Drug Administration (FDA) suggests adding enough folic acid to food to fortify it. Folic acid at a daily dose of 0.4 mg, which is typically found in over-the-counter multivitamin products, lowers the risk of NTDs by around 60% during the peri-conceptional period. In order to lower their risk of having a pregnancy impacted by spina bifida or other NTDs, the US Public Health Service (PHS) advises that all women in the US of childbearing age who are capable of becoming pregnant ingest 0.4 mg of folic acid daily Care should be taken to limit total folate intake to 1 mg per day because the effects of large intakes, which may include obscuring the diagnosis of vitamin B12 deficiency, are not fully understood. A subsequent impacted pregnancy is highly likely for women who have already experienced an NTD.

3.1 Phenytoin (hydantoin, Dilantin):

A drug called phenytoin is used to treat epilepsy. There is a minor risk for the foetal hydantoin syndrome, a group of birth abnormalities, if the mother uses it during the first trimester. Developmental delay or blatant mental disability, dysmorphic craniofacial traits, and hypoplasia of the distal phalanges make up the pattern of defects. Major phenytoin-related birth abnormalities are correlated with lymphocytes' inability to metabolise the medication. The risk of phenytoin foetal toxicity appears to be hereditary. The hydantoin syndrome's signs have not always occurred in tandem in twins. Children exposed to phenytoin run the risk of developmental disruption anywhere from 1% to 11%. A maximum of 10% risk for the entire syndrome and a maximum of 30% risk for specific anomalies is shown by chronic exposure.

3.2 Warfarin (dicumarol, coumarin derivatives):

Long-term anticoagulant medication is frequently necessary for women who have a history of thromboembolic disease or mechanical heart valves. After exposure throughout the eight to fourteen weeks of pregnancy, there is a 25% chance for afflicted infants. Warfarin prevents glutamyl residues from becoming carboxyglutamyl, which reduces proteins' capacity to bind calcium. Choanal stenosis could happen. In the tarsals, proximal femurs, and paravertebral processes, calcific stippling is most prevalent. About half of affected infants have brachydactyly and tiny nails, with the upper limbs being more severely affected. Exposure in the first or second trimester can cause optic atrophy, microphthalmia, and blindness. Microcephaly, optic atrophy, visual impairment, seizures, hypotonia, and mental retardation are a few examples of brain malformations. The nasal hypoplasia, stippled calcification, and skeletal abnormalities of warfarin embryopathy may be explained by proteins inhibiting calcium binding during a crucial stage of ossification.

3.3 Trimethadione, paramethadione:

In one-fourth of pregnancies, maternal usage of these medicines causes a spontaneous abortion. Prenatal and postnatal growth deficiencies, developmental delays, malformations, and distinctive facies are present in the majority of liveborn infants. These features include brachycephaly with midfacial hypoplasia, V-shaped eyebrows with or without synophrys, broad nasal bridge, arched or cleft palate, and malpositioned ears with anterior cupping and/or excessive folding of the superior helices. Renal malformations, tracheoesophageal abnormalities, hernias, and hypospadias are all common cardiovascular defects, especially septal defects and tetralogy of Fallot. Mild to moderate mental retardation and verbal impairment are common in survivors.

3.4 Cocaine:

Because the foetus has low plasma cholinesterase activity, cocaine is metabolised relatively slowly in the foetus. Cocaine inhibits neurotransmitter presynaptic reuptake in nerve terminals, causing norepinephrine and dopamine levels to rise. Calcium availability and utilisation may be affected, and blood flow from the uterus to the placenta may be decreased. Vascular disruption seems to be a factor in the problems of abruptio placentae, cerebral haemorrhage, IUGR, limb abnormalities, bowel atresia, and necrotizing enterocolitis. There are also higher rates of

preterm, microcephaly, and sudden infant mortality in foetuses exposed to cocaine.

3.5 Statins:

When someone has cardiovascular disease or is at risk for it, statins are hypolipidemic medications that lower serum cholesterol levels. The enzyme that catalyses the creation of mevalonate from HMG-CoA, the rate-limiting step in the mevalonate route of cholesterol biosynthesis, is 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase, which statins block. Since cholesterol is a necessary component of cell membranes, it plays a crucial role in foetal and embryonic development. It is also a precursor to steroid hormones and necessary for the activation and spread of hedgehog signalling, which controls crucial developmental processes like CNS patterning. These medications are contraindicated for use in women who are or may become pregnant because the FDA classified them as being in pregnancy category X. Early pregnancies may unwittingly be exposed to them because over 50% of pregnancies in the United States are unplanned.

Concern has been expressed about the possible impact of prenatal statin use on embryonic and foetal development due to the detection of numerous patterns of congenital abnormalities (CA) brought on by inadequate de novo cholesterol synthesis. These patterns include the Smith-Lemli-Opitz syndrome; two Smith-Lemli-Opitz-like syndromes, desmosterolosis and lathosterolosis; and two skeletal dysplasia syndromes with dermatologic manifestations, X-linked dominant chondrodysplasia punctata type 2 and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (Child syndrome). Statins are not yet known to be teratogenic in humans, according to controlled investigations. Statins may have teratogenic effects, according to case studies and a case series published by Edison and Muenke.

3.6 Ethanol, Smoking, and Various Drugs causes Teratogen:

Fetal Alcohol Syndrome (FAS).

Foetal alcohol syndrome (FAS) has been observed in children of alcoholic mothers and is characterised by substantial physical retardation that begins during pregnancy and persists beyond birth.Strict standards for diagnosing FAS have been established by the Research Society on Alcoholism's Foetal Alcohol Study Group. For a diagnosis of the syndrome to be considered valid, at least one trait from each of the three categories below must be present: (1) growth retardation before or after birth; (2) facial anomalies, such as small palpebral fissures, indistinct or absent philtrums, epicanthic folds, flattened nasal bridges, short noses, thin upper lips, and delayed midfacial development; and (3) central nervous system dysfunction, such as

microcephaly, varying degrees of mental retardation, or other signs of abnormal neurobehavioral development, such as attention deficit disorder.

Up to 50% of infants born to heavily drinking alcoholic mothers have structural and functional abnormalities. Infants whose mothers drink moderately (1 to 2 oz of absolute ethanol daily) can experience functional and development abnormalities without additional morphologic alterations. Infants of moms who consume less than one ounce of absolute ethanol each day have not been shown to have any birth defects. But among women who use 1 oz. of ethanol twice a week, the chance of spontaneous abortion is double the average rate. Fetotoxicity may result from binge drinking in the first trimester. Abstinence from alcohol during pregnancy is a reasonable precaution due to the limited knowledge of the effects of prenatal exposure to alcohol.

IV Tobacco smoking:

Through reduced perfusion of foetal tissues, nicotine, a vasoconstrictor, causes uterine vascular constriction and intrauterine growth retardation (IUGR). It is a component of tobacco and a cholinergic agonist. The risk of perinatal death and morbidity increases with cigarette smoking throughout pregnancy. Abruptio placentae, placenta previa, spontaneous miscarriage, preterm, and IUGR are blamed for the higher mortality.

Additionally, carbon monoxide from cigarette smoke crosses the placenta and raises blood levels of carboxyhemoglobin (HbCO); foetal blood has a longer half-life of HbCO than does maternal blood.

4.1 Lysergic acid diethylamide (LSD):

Several malformations have been observed in children born to moms who used LSD prior to or during pregnancy. There could be arthrogryposis, limb, ocular, and CNS defects. Since the women's lifestyle may include the use of alcohol and other drugs, subpar medical care, and starvation, determining the effects of LSD usage during pregnancy has proven to be challenging. There is no evidence to suggest that there is a high risk of congenital abnormalities. Chromosome damage brought on by LSD can remain for up to two years, but it can also be temporary. There is no proof that paternal small-dose LSD exposure before conception increases the risk of spontaneous abortion, preterm birth, or birth abnormalities**.**

Isotretinoin **(Accutane, retin-A, retinoic acid):**

When a pregnant woman takes isotretinoin, there is a 25% chance of foetalabnormalities . 4 to 10 weeks of gestation constitute the key exposure period. These defects include hypoplastic

adrenal cortex, hydrocephalus, microcephaly, cerebellar dysgenesis, depressed nasal bridge, microtia or absent external ears, cleft palate, anomalies of the aortic arch, and cardiac defects (including ventricular septal defect, atrial septal defect, and tetralogy of Fallot). Abortion that occurs at random is also rising.Women of childbearing age receiving isotreitinoin have a pregnancy prevention programme in place. There is no evidence linking topical retinoic acid use to foetal abnormalities. Etretinate can result in skeletal, cardiovascular, and CNS abnormalities, just like its congener isotretinoin. Etretinate is linked to lipoproteins and stays in the bloodstream for years after use, in contrast to isotretinoin.

V CONCLUSION:

The teratogenic effects of drugs during pregnancy are a significant concern that healthcare providers and pregnant women should be aware of. It is essential to weigh the potential risks and benefits of using any medication during pregnancy, and if possible, avoid exposure to teratogens during the critical periods of fetal development. Consult with your healthcare provider before taking any medication during pregnancy.Patients should be educated about methods other than drugs to cope with tension, aches and pains, and viral illnesses during pregnancy. The risk-to-benefit ratio should justify the use of any drug and the minimum effective dose should be used. Patients should be educated about risks of social drug exposure. Because long-term effects of drugs *in utero* may not be revealed for many years, caution with regard to any drug use in pregnancy is warranted.

VI FUTURE SCOPE

Development of predictive fashions: Advanced computational fashions, together with system gaining knowledge of and synthetic intelligence, can assist expect and perceive ability teratogenic consequences of medication with more accuracy. These fashions can examine big datasets and don't forget a couple of elements to offer greater particular danger exams. Biomarkers for teratogenicity: Research may also cognizance on figuring out precise biomarkers which can imply the teratogenic ability of medication. Biomarkers will be genetic, epigenetic, or biochemical markers that assist expect an man or woman's susceptibility to teratogenic consequences. Personalized medicinal drug strategies: With advances in genetic checking out and information man or woman variability, there may be ability for customized medicinal drug strategies to decrease teratogenic risks. Tailoring drug choice and dosages primarily based

totally on a person's genetic profile may also assist lessen the possibilities of detrimental consequences at some point of being pregnant. Drug repurposing: The research of current pills which have already passed through protection checking out for different situations can be explored for ability use in being pregnant. This technique ought to assist perceive more secure options for pregnant ladies whilst decreasing the danger of teratogenic consequences. Long-time period follow-up research: Conducting long-time period research to display the effects of youngsters uncovered to doubtlessly teratogenic pills in utero can offer treasured insights into the long-time period consequences and improvement of those individuals. Such research can assist refine danger exams and tell destiny remedy decisions. Lifestyle interventions: Future studies may also discover the effect of life-style interventions, together with diet, exercise, and pressure reduction, on mitigating the teratogenic consequences of sure pills. Understanding how life-style elements engage with drug exposures at some point of being pregnant can offer extra techniques for minimizing risks. Patient training and awareness: Enhancing public and affected person training approximately the teratogenic consequences of medication, together with the significance of preconception care and right medicine use at some point of being pregnant, can play a enormous position in stopping avoidable exposures and enhancing maternal and fetal fitness effects.

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