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

Tetatogenic 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 toform onecell, development begins. Pregnancy lasts for 9 weeks, which are split into threetrimesters, andis known as the embryogenesis phase for the first 8 weeks of human development. This period isalso referred to as the organogenesis period. Because all medications taken by the female havethe potential to have negative effects on the developing foetus or nursing baby, pregnancy andlactation constitute a unique clinical setting where drug therapy raises significant concerns.Thefirst trimester of pregnancy is when medicines can do the most harm. Around the world, birthabnormalities cause the deaths of almost 3.3 million children under the age of five every year.Following the horrors of the thalidomide pandemic in the 1970s and the rubella epidemic intheearly 1960s, interest in the field of teratology sought attention. Drugs includingchloramphenicol, warfarin, valproate, and thalidomide can cause anomalies such microcephaly,hydrocephalus, phocomelia, spina bifida, and a number of syndromes. Teratogenicity cannot betreated, but it can be avoided by abstaining from dangerous medicines and taking thenecessarysafety 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 anembryo'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 duration of teratogen exposure during pregnancy, the dosage, and the genetic

vulnerability of the developing foetus all have an impact on the results. 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.

As an illustration, in the early 1960s, thalidomide was given to treat morning sickness..Due to exposure of the embryo at this formative stage of development, cases of phocomelia, a congenital condition in which the hands and feet are joined to short arms and legs, have been reported. The types or severity of defects resulting from a teratogenic substance can be determined by the genetic susceptibilities of the mother and foetus. For example, variations in the maternal metabolism of a particular medicine will affect the quantity of metabolites the foetus is exposed to and the length of time it is exposed to them. The outcome will also be influenced by the foetus' genetic susceptibility to a certain teratogenic substance.

DRUGS AND BIRTH DEFECTS

When assessing the clinical consequences of pharmaceutical teratogens, it is important to take into account the whole context of developmental disorders in humans. Defects may have unknown or inherited causes. There is evidence that 25% of them have genetic (chromosomal, Mendelian, etc.) underpinnings. Despite the reason of about 65% of abnormalities is ostensibly unknown, they are likely the result of both genetic and environmental factors (polygenic/multifactorial). The risk for deformity following exposure to a drug must be contrasted with the background rate, which is commonly estimated as being between two and three percent for significant deformities in the general population. Serious abnormalities that are incompatible with survival and need extensive surgery to treat include anencephaly, cleft palate, congenital heart disease, or major dysfunction (such as mental retardation).

Almost every chemical that the woman consumes while she is expecting has the potential to be teratogenic and harmful to the unborn. Almost all chemicals that are lipid-soluble pass through the placenta without any issues. A material may travel through water more easily when it has a lower molecular weight.The quantity of a medication that is bound to plasma protein affects how much of the drug is free to pass the placenta.The exception being large organic ions like fractionated and unfractionated heparin and insulin, the majority of medications pass the placenta to some extent.

II. VARIABLES 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) With low dosages, there is no impact; (2) At moderate levels, a pattern of organ-specific abnormalities may develop; or (3) High dosages may destroy the embryo, preventing the detection of the organ-specific teratogenic activity.Teratogens often have an effect on animals at doses that are between a fourth and a half of what it takes to kill the mother. The stage of development that 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.

Stage of Embryonic Development:

Determining the exact moment, a possible teratogen is delivered to the developing foetus is crucial. Each organ system experiences vulnerability at a different moment throughout three distinct phases.

(1) The embryo is generally resistant to teratogenic insults in the first few weeks of life, maybe two weeks after conception in humans.Although a severe injury may kill the embryo, survivors typically show no organ-specific abnormalities. Since early embryonic cells have not irrevocably differentiated, it is hypothesized that this is the cause. If one cell is eliminated, a survivor may be able to seize control.

(2) The bulk of human organ systems undergo organogenesis, or the process of organ differentiation, between embryonic weeks 3 and 8 (menstrual weeks 5–10); the brain and gonads, however, develop later.Tolerance to teratogens peaks throughout organogenesis. Teratogens work in a way that is distinct to each organ; they may affect one organ system at one stage of development but another system at a subsequent level. Thus, both whether a deformity will occur and the specific spectrum of aberrations depend on the damage's timing.

(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 example, giving androgens to a pregnant woman after the 12th week may cause the female foetus to develop in the clitoral region but not at the urethral opening or the labioscrotal folds.An older foetus is

often adversely affected by a drug that adversely affects a newborn. Anomalies can also be the result of side effects.

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. This method makes the most sense when the three steps of drug catabolism—maternal capacity to absorb or metabolize a teratogen, placental transfer, and foetal metabolism—are taken into account. 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 decarboxylate (catabolize) medications like Isoniazid or hydralazine. Comparatively, an altered allele may hinder a foetus from protecting itself against a potential teratogen. Thus, the administration of a particular teratogen may have negative effects on that foetus but not on other (normal) foetuses.

Drug Interactions:

When two teratogens are administered simultaneously, the results may differ from when they are administered individually. For instance, folic acid prevents the teratogenesis that cortisol causes in mice, maybe as a result of the stimulation of enzyme systems that either degrade or compete with the teratogen for binding sites. On the other hand, one substance might increase the teratogenic potential of another. For instance, the food preservative benzoic acid increases the rat teratogenicity of aspirin. Potential mechanisms that, if present, might reduce quantities of the unbound active teratogen include the inhibition of enzymes, the elimination of cells that make enzymes, and the saturation of binding sites on carrier proteins.

III. 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, oesophageal and duodenal atresia, tetralogy of Fallot-like heart malformations, renal agenesis, urinary tract anomalies, vaginal defects, dental anomalies, ear anomalies, facial palsy, ophthalmoplegia, anophthalmia, microphthalmia, and coloboma, among other anomalies. 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. The majority of them were limb abnormalities, commonly with preaxial polydactyly with six or seven toes per foot and ranged from triphalangeal thumb to tetra Amelia or phocomelia of the upper and lower limbs. About 20% of pregnancies exposed at this time resulted in babies with anomalies.

Fig 1: THALIDOMIDE EFFECT

McCredie hypothesised that disruption of neural crest-based sclerotomalorganisation was the pathogenetic basis of the limb abnormalities. McCredie and colleagues expanded their studies of the visceral anomalies in infants who died with multiple congenital anomalies and longitudinal limb defects 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. When the autopsy data were applied to sclerotomal and viscerotomal maps, 89% of cases had a neuroanatomic link. The authors proposed a developmental connection within a multiple congenital abnormalities syndrome based on neurotomes or embryonic developmental fields with common regional innervation. Thalidomide inhibits angiogenesis, and its teratogenicity is correlated with its antiangiogenic effect.

Folic acid antagonists and folic acid deficiencies:

Folic acid deficits have been found in many mothers who have given birth to infants with neural tube abnormalities (NTDs).; 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, which is generally included in over-the-counter multivitamin supplements, reduces the incidence of NTDs by around 60% during the peri-conceptional phase at a dose of 0.4 mg per day..The US Public Health Service (PHS) recommends that all US women of childbearing age who are capable of becoming pregnant consume 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 obfuscating 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.

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. The pattern of anomalies includes hypoplasia of the distal phalanges, dysmorphic craniofacial characteristics, and developmental delay or obvious mental retardation. The failure of lymphocytes to metabolize phenytoin is associated with severe birth defects. The risk of phenytoin foetal toxicity appears to be hereditary. The hydantoin syndrome's signs have not always occurred in tandem in twins. Between 1% and 11% of children exposed to phenytoin may have developmental impairment. Chronic exposure indicates a maximum 10% risk for the complete syndrome and a maximum 30% risk for particular defects.

Warfarin (dicumarol, coumarin derivatives):

For female patients with a history of artificial heart valves or thromboembolic illness, long-term anticoagulant therapy is typically required.. 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. Calcific stippling is most common in the tarsals, proximal femurs, and paravertebral processes. 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. Examples of brain

abnormalities include microcephaly, optic atrophy, visual impairment, seizures, hypotonia, and mental retardation..It is possible that proteins blocking calcium binding during a critical period of ossification are responsible for the nasal hypoplasia, stippled calcification, and skeletal abnormalities of warfarin embryopathy.

Trimethadione, paramethadione:

In one-fourth of pregnancies, maternal usage of these medicines causes a spontaneous abortion. The majority of liveborn newborns have prenatal and postnatal growth deficits, developmental delays, deformities, and unique facies. Brachycephaly with midfacial hypoplasia, V-shaped eyebrows with or without synophrys, a large nasal bridge, an arched or cleft palate, and malpositioned ears with anterior cupping and/or excessive folding of the superior helices are some of these characteristics.Common cardiovascular problems include renal malformations, tracheoesophageal abnormalities, hernias, and hypospadias, notably septal defects and tetralogy of Fallot. Mild to moderate mental retardation and verbal impairment are common in survivors.

Cocaine:

Cocaine is metabolized very slowly in the embryo due to poor plasma cholinesterase activity. Cocaine inhibits neurotransmitter presynaptic reuptake in nerve terminals, causing norepinephrine and dopamine levels to rise. Blood flow from the uterus to the placenta may be reduced, and calcium availability and utilization may be impacted.Abruptio placentae, brain haemorrhage, IUGR, limb deformities, bowel atresia, and necrotizing enterocolitis appear to be issues caused by vascular disruption. There are also higher rates of preterm, microcephaly, and sudden infant mortality in foetuses exposed to cocaine.

Statins:

When someone has cardiovascular disease or is at risk for it, statins are hypolipidemic medications that lower serum cholesterol levels. Statins inhibit 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the formation of mevalonate from HMG-CoA, the rate-limiting step in the mevalonate pathway of cholesterol production.Since cholesterol is required for the formation of cell membranes, it is extremely important for the growth and development of foetuses and embryos.Additionally, it functions as a precursor to steroid hormones and is important for the activation and propagation of hedgehog signaling, which regulates critical developmental processes such 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. Because more than 50% of pregnancies

in the United States are unplanned, early pregnancies may unintentionally be exposed to them.

Due to the identification of multiple patterns of congenital abnormalities (CA) caused by insufficient de novo cholesterol synthesis, concern has been raised concerning the potential effects of prenatal statin usage on embryonic and foetaldevelopment..Two skeletal dysplasia syndromes with dermatologic manifestations are X-linked dominant chondrodysplasia punctata type 2 and congenital hemidysplasia with ichthyosiform erythroderma and limb defects (Child syndrome), in addition to the Smith-Lemli-Opitz syndrome and two Smith-Lemli-Opitz-like syndromes, desmosterolosis and lathostero. Statins are not yet known to be teratogenic in humans, according to controlled investigations.

Teratogens are caused by ethanol, smoking, and many drugs.:

Fetal Alcohol Syndrome (FAS).

Children of alcoholic mothers have been shown to have the foetal alcohol syndrome (FAS) 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) birth defects or postnatal growth retardation; (2) abnormalities of the face, including tiny palpebral fissures, philtrums that are unclear or missing, epicanthic folds, flattened nasal bridges, short noses, thin upper lips, and delayed midfacial development; and (3) disorder of the central nervous system, such as Other indications of aberrant neurobehavioral development, such as attention deficit disorder, include microcephaly, various levels of mental impairment, or other conditions.

Babies born to extremely intoxicated, alcoholic mothers can have structural and functional defects in up to 50% of cases. Without further morphologic changes, infants whose moms regularly drink (1 to 2 oz of absolute ethanol daily) might have functional and developmental issues. Infants of moms who consume less than one ounce of absolute ethanol each day have not been shown to have any birth defects. However, the likelihood of spontaneous abortion is double the usual incidence among women who consume 1 oz. of ethanol twice per week. First trimester excessive drinking may cause foetal poisoning. Due to the limited understanding of the consequences of prenatal alcohol intake, abstaining from alcohol throughout pregnancy is a sensible precaution.

Tobacco smoking:

Nicotine, a vasoconstrictor, promotes uterine vascular constriction and intrauterine growth retardation (IUGR) by reducing the perfusion of foetal tissues. 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, the placenta is crossed by carbon monoxide from cigarette smoke, which increases blood levels of carboxyhemoglobin (HbCO). HbCO has a longer half-life in foetal blood than it does in maternal blood.

Lysergic acid diethylamide (LSD):

Children born to mothers who took LSD before or during pregnancy have been shown to have a number of abnormalities. There could be arthrogryposis, limb, ocular, and CNS defects. Determining the consequences of LSD use during pregnancy has proven to be difficult since the women's lifestyle may involve the use of alcohol and other drugs, poor medical care, and hunger. There is no proof to support the notion that the risk of congenital defects is considerable. LSD-induced chromosomal damage can last for up to two years, but it can also be transient. 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. The 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 (such as ventricular septal defect, atrial septal defect, and tetralogy of Fallot) are among these defects. Abortion that occurs at random is also rising.Those receiving isotreitinoin who are of reproductive age have access to a pregnancy prevention service. There is no evidence linking topical retinoic acid use to foetal abnormalities. Like its congener isotretinoin, etretinate can cause problems in the CNS, cardiovascular system, and skeletal system. In contrast to isotretinoin, etretinate is attached to lipoproteins and remains in the circulation for years after usage.

IV. CONCLUSION

The teratogenic effects of drugs during pregnancy are a significant concern that healthcare providers and pregnant women should be aware of. The potential dangers and advantages of using any drug while pregnant must be carefully considered. If at all possible, avoid being exposed to teratogens during the crucial times for foetal development. Consult with your healthcare provider before taking any medication during pregnancy. Patients should be informed about natural ways to deal with stress, aches and pains, and viral diseases during pregnancy without using medication. Any medicine should only be taken when the risk to benefit ratio supports it, and the lowest effective dose should be used. Patients need to be informed of the

dangers of social drug exposure. It is advisable to use caution while using any medicines when pregnant because the long-term effects of using them in utero may not become apparent for many years.

V. 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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