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TERATOGENIC EFFECT OF DIFFERENT DRUGS AT DIFFERENT STAGES OF PREGNANCY.

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ABSTRACTS:-

Teratogenic effects of drugs are stage-dependent during pregnancy, influencing fetal development at critical periods. In the first trimester, organogenesis occurs, making the embryo vulnerable to major malformations from teratogen exposure. The second trimester poses lower risks for structural anomalies but can impact organ growth and functionality. In the third trimester, drug exposure may affect fetal development and lead to behavioral or cognitive issues. Understanding these stages is essential for ensuring maternal and fetal safety while managing pharmacological treatments.

KEYWORD'S :-

Eratogenesis, Pregnancy stages, First trimester, Second trimester, Third trimester, Fetal development, Drug exposure, Maternal health

1.INTRODUCTION :-

Pregnancy-related alterations in the mother's physiology and the possibility of teratogenic effects from the drug make pharmacological therapy particularly concerning [1,7]. Pregnancy results from the sperm entering an egg. Fertilization is the term for this process, which frequently occurs in the female fallopian tube. Immediately after fertilization, the egg begins to divide, producing an enormous mass of cells. A placenta is formed when the fertilized egg implants into the uterine wall five to seven days following ovulation [2]. During the first eight weeks of pregnancy, drugs mainly affect the development of the human embryo. For the first week, the blastocyst is unrestricted in its movement within the uterus and is dependent on uterine secretions for nourishment. Exogenous substances such as drugs may cause the embryo to die, although it is yet uncertain if they can induce congenital defects [3]. The FDA established the A, B, C, D, or X risk classifications in 1979 to denote a drug's

potential to result in birth abnormalities if taken while pregnant [5]. Teratogenicity is the term used to describe the development of abnormalities in the fetus. Such a defect is brought about by a teratogenic medication.

1.1 STAGES OF PREGNANCY :-

First Trimester:- 1 to 3 Months (Week 1 through 12) :-

The 12-week first trimester begins at fertilization. Typically, a pregnancy follows this path for the first three months. The fertilized egg will develop throughout this trimester from a small clump of cells into a fetus that is starting to show signs of human identity [3]. While the first trimester might be enjoyable, most people also experience uncomfortable symptoms like exhaustion and morning sickness at this time [5].

Second Trimester :- 4 to 7 Months (Week 13 Through 28)

Most people consider the second trimester of pregnancy to be the greatest. Any morning sickness and any discomfort from the early stages of pregnancy should have subsided by now. Additionally, when the fetus turns and spins inside your uterus, you can begin to feel movement. [1].

Third trimester: - 8 to 10 Months (weeks 29 through 40)

This is the last phase of your pregnancy. Refrain from giving in to the urge to start marking off the days before your due date in the hopes that it will arrive earlier. The fetus gets ready to be born with every week of this last stage of growth. The fetus increases weight quickly in the third trimester and accumulates body fat that will be useful after delivery [6].

1.2 STAGES OF EMBRYONIC DEVELOPMENT:-

Determining the exact moment a possible teratogen is delivered to the fetus during development is crucial. There are three discernible stages of susceptibility, with varying temporal correlations for every organ system:-

(1) The embryo is largely resistant to teratogenic insults during the first few weeks of life, maybe two weeks after conception in humans.2. Severe damage can kill the embryo, although most survivors do not have defects specific to any organ. The lack of irreversible differentiation in early embryonic cells is thought to be the cause. One cell may be able to take control of another if it is destroyed.

(2) Most human organ systems go through organogenesis, or the process of organ differentiation, between embryonic weeks 3 and 8 (menstrual weeks 5–10); the brain and gonads, on the other hand, develop later. The peak of susceptibility to teratogens occurs during organogenesis. Teratogens affect an organ's systems differently depending on the stage of development; they may affect an organ's systems differently at different times. Therefore, the precise time of the damage affects the range of aberrations as well as whether a deformity develops.

(3) The primary characteristic of embryonic development after organogenesis is a rise in organ size. Eight to ten embryonic weeks precede the bulk of human organ systems in this time frame. During this period, a teratogen may affect the size of an organ or the overall growth of the embryo. Nevertheless, evident flaws are not expected. For example, giving androgens to a pregnant woman beyond the 12th week of her pregnancy may cause the female fetus to grow at the clitoral region, but not the urethral opening to move or the labioscrotal folds to fuse. Generally speaking, an older fetus is adversely affected by the same medicine that harms a newborn. Side effects may potentially be the cause of anomalies.

1.3 GENOTYPE :-

There are two well-established genetic pathways—monogenic or Mendelian inheritance and polygenic inheritance—that could plausibly account for differences in genetic vulnerability. Individual differences in drug use, and hence individual differences in teratogenic susceptibility, are probably polygenic. It is assumed in polygenic inheritance that a trait is influenced by the combined action of several genes. The genotypes contribute to continuous fluctuation in genetic liability. This method makes the most sense when the three steps of drug catabolism—placental transfer, fetal metabolism, and maternal ability to absorb or metabolize a teratogen—are taken into account. Adult monozygotic twins manage drugs more similarly than dizygotic twins, but not identically enough for a single gene to account for the differences. Nonetheless, monogenic variables do occur.
In a tiny percentage of individuals, a single mutant allele may provide resistance to or increased susceptibility to specific drugs. These individuals are diagnosed with a pharmacogenetic illness. Lack of pseudocholinesterase, resistance to heparin and warfarin, and an incapacity to catabolize (decarboxylate) drugs such as isoniazid or hydralazine are a few examples. In contrast, a mutant allele can make it impossible for a developing foetus to neutralize a potential teratogen. Consequently, the delivery of a specific teratogen might be detrimental to that fetus but not to other (normal) fetuses.

1.4 DRUG INTERACTION :-

There may be differences in the outcomes between the simultaneous administration of two teratogens and their individual administration. For example, folic acid decreases the teratogen's ability to bind to binding sites in mice8 when exposed to cortisol. This may be due to the stimulation of enzyme systems that either break down or rival the teratogen. Conversely, a chemical may make another more teratogenic-prone. Benzoic acid, a food preservative, for example, increases the rat teratogenicity of aspirin. Should these mechanisms occur, they could reduce quantities of the unbound active teratogen. These actions include inhibition of enzymes, elimination of cells that make enzymes, and saturation binding sites on carrier ptprotein

2.DRUGS AND THEIR TERATOGENIC EFFECTS :-

2.1 Anticonvulsant/Antiepileptic Drugs

Carbamazepine (CBZ), an anticonvulsant and mood stabilizer, is mostly used to treat epilepsy, bipolar disorder, and trigeminal neuralgia. Because it works so well, pregnant women often use this medicine. well tolerated and thought to be quite safe during pregnancy when compared to other antiepileptie drugs (AEDs) [9]. Children of epileptic women are more likely to have major congenital abnormalities (4% to 10%), which is 2–4 times more common than the estimated frequency in the general population [10].Wilson has emphasized the significance of developmental age, the significance of inherited vulnerability, and the range of effects of drug with many proposed teratogenicity mechanisms. However, several researches have suggested that phenobarbital and carbamazepine may be less harmful teratogenic agents than phenytoin for animals [11].Less is known about the risks that maternal seizures pose to the foetus, but generalized tonic-clonic seizures can cause hypoxia and lactic acidosis in the foetus, as well as status epilepticus which can result in foetal death [12].Certainly, the increasing

body of knowledge on differences in teratogenic potential across AEDs has altered drug selection for reproductive age women with epilepsy. The most useful study was the Prospective Neuro Development Effects of Antiepileptic Drugs (NEAD trial), which included early-pregnant women receiving monotherapy with valproate, carbamazepine, lamotrigine, and phenytoin [13]. Because many teratogenic antiepileptic medicines are also used to treat psychiatric diseases, migraine headaches, and neuropathic pain, there is a risk of exposure for pregnancies with maternal health issues other than epilepsy [14].Numerous small-scale studies have already assessed the possibility that exposure to AED during pregnancy may have a deleterious effect on the postnatal development of the offspring. The specific conditions of each patient, such as the kind of epilepsy, the frequency of seizures, and their socioeconomic status—all of which raise the possibility of malformations—determine the appropriate dosage or choice of AED (15).

2.2. Antibiotic drugs

In some cases, such as the treatment of asymptomatic bacteriuria to prevent ascending infection and bad pregnancy outcomes associated to pyelonephritis, antibiotic medicine can be both effective and life-saving. Among these were tetracycline, kanamycin, and streptomycin, which have the potential to cause hearing loss, which can subsequently weaken, hypoplasia, and discolor long bones and teeth [16]. When treating a serious bacterial infection, cephalosporin antibiotics are commonly given orally and parenterally. With a low apparent degree of toxicity and a wide variety of effects, cephalosporins have been created throughout the course of three generations. "There are no known epidemiological studies of congenital malformations among offspring of women treated with cephalaxin during pregnancy," expressed Friedmann and Polifka in 1996. The same finding was made for cefaclor, cefadroxil, and cefluroxamine as well.(17) Because tetracyclines are on the list of known human teratogens, they are not allowed to be taken while pregnant. Right now, doxycycline is the most often used derivative of tetracycline and is also very affordable. Doxycycline is also used in the treatment of sexually transmitted infections (SFIs), including syphilis, Chlamydia, and pelvic inflammatory disease. To the best of our knowledge, there is no evidence linking the use of doxycycline during pregnancy to teratogenic effects in humans. Regretfully, after doxycycline was developed, tetracycline was labeled as possibly hazardous because of severe adverse effects, such as teratogenicity [18, 19].

Since the thalidomide disaster, there has been a significant increase in public awareness of the risks associated with drug use during pregnancy. A prospective study of pregnant women, on the other hand, found that all participants had taken at least two medications, and 93% had taken five or more. Antibiotics were responsible for roughly 37% of the medications utilized [20]. Pregnant women were most commonly prescribed the aminopenicillin family antibiotic ampicillin. Because ampicillin passes through the placenta fast and reaches the fetal circulation and amniotic fluid, it can be detected in foetal serum within 30 minutes. As a result, it may cause birth defects related to the heart and blood vessels [21].

2.3 Anticancer drug :-

The beginning of 1978 saw the confirmation of the pregnancy. The patient was made aware of the potential for teratogenic effects on the foetus and the probability of recurrence without maintenance. Distal limb anomalies were the sole physical findings that were abnormal. The distal phalanges of both thumbs were absent, and the right thumb's remnants was remarkably hypoplastic [22]. Natural chemicals and their analogs, such as doxorubicin, daunomycin, paclitaxel, and vinblastine, are the cornerstones of cancer chemotherapy. The use of anticancer drugs in the therapy of cancer is limited due to their harmful effects, as they target targets present in

all normal calls. Adult women are unaffected by these teratogens, but embryos may be at risk [23].The efficacy of chemotherapy in treating cancer in humans has increased during the last three decades [24]. Thalidomide differs from these chemically comparable counterparts in that it has sedative properties as well as a wide spectrum of immunomodulatory and anticancer actions. Because of the asymmetric carbon that gives the molecule its optical activity, thalidomide is racemic, including equal proportions of the left- and right-handed optical isomers International Journal of Pharma Research and Health Sciences [25]. Currently marketed as anticancer drugs are two well-known teratogens: thalidomide and arsenic. Thalidomide helps with multiple myeloma treatment. In addition, thalidomide was used to "cure" morning sickness in pregnant women—the very condition that the drug was intended to prevent [26].As part of the treatment for ectopic pregnancy, a woman who is already known to be pregnant is given methotrexate. If a woman receiving treatment while carrying both an intrauterine and an ectopic pregnancy, or if an ectopic pregnancy is misdiagnosed in a woman who is already carrying a baby inside her uterus, she may be exposed to methotrexate during her continuing pregnancy [27].

2.4 HIV drugs :-

Mother-to-child transmission is the cause of almost 90% of all HIV infections in infants and young children. This trial showed that zidovudine
(azidodeoxythymidine, or AZT) reduced vertical HIV transmission by two-thirds in the absence of nursing when treated as intense monotherapy during pregnancy and delivery and given orally to newborns for six weeks after birth [28]. Women living with HIV/AIDS make up a substantial portion of the potential study subjects for a number of novel drugs under investigation. The natural history of the illness may not affect women in the same way [29]. The pharmacokinetics of antiviral drugs may also be impacted by pregnancy-related physiological changes, such as blood volume expansion and gastrointestinal, enzymatic, and hormonal alterations. These modifications may lead to modified absorption, reduced protein binding, and elevated and increased elimination [30].Pregnant women with active Ols who use drugs for which there is insufficient data about their use during pregnancy ought to have their fetal growth and well-being further assessed [32]. A cooperative pharmaceutical industry endeavor, the Antiretroviral Pregnancy Registry was designed to prospectively identify any substantial teratogenic effect involving any of the ARV drugs that pregnant women are exposed [33]. However, it was not recommended to use antiretroviral therapy during fetal embryo organogenesis, which occurs before 14 weeks, due to the possible teratogenic consequences of the antiretroviral medications [34]. Antiretroviral therapy for expectant HIV-positive women Access to women is necessary to prevent HIV transmission during pregnancy. regimens with a stronger antiviral effect that include protease inhibitors (PI) and zidovudine (ZDV) [35].

2.5 Thyroid drugs

Hyperthyroidism is one of the most common endocrine disorders affecting expectant mothers, and it can have a significant impact on the course and outcome of a pregnancy [36]. A serious condition known as pregnancy-related hyperthyroidism raises the possibility of unfavorable obstetric outcomes such as intrauterine growth restriction, stillbirth, miscarriage, and preterm birth. Antithyroid drugs (ATDs) have been prescribed since the 1940s and are the recommended treatment during pregnancy [37]. Hyperthyroidism during pregnancy increases the risk of severe pre-eclampsia or placental abruption [38].Thyrotoxicosis, most usually caused by Graves disease (GD), occurs in around 0.2% of pregnancies. The three available treatments for Graves disease are surgery, radioactive iodine therapy, and pharmaceutical therapy utilizing antithyroid drugs (ATDs). Using radioactive iodine to treat maternal GD while you are pregnant is not encouraged. The risk of miscarriage is

associated with surgery. For this reason, ATDs are the recommended course of treatment for GD in pregnancy [38–40]. The best treatment for hyperthyroidism during pregnancy is therefore ATDs at the lowest therapeutic doses, which also demonstrate the transfer of TSH, thyroid hormones, TRAb, and ATDs from the mother's to the fetus's circulation [41].

2.6 Analgesic drugs

The most common and conventional nonsteroidal anti-inflammatory analgesic is aspirin. High-dosage aspirin users throughout pregnancy seem to give birth to babies that weigh significantly less. Therapeutic standard doses don't seem to affect the newborn's birth weight or the mother's health [42]. Based on gestation week, the obstetricians' antenatal care logbook, and the drugs taken during pregnancy [43]. It is challenging to determine the prevalence of NSAID use during pregnancy because some of them are available over-the-counter (OTC) and do not require a prescription. Chronic rheumatic diseases such as spondyloarthritis and rheumatoid arthritis, as well as inflammatory bowel disorders, are markers of long-term NSAIDS usage during pregnancy [44]. Medication taken by mothers and illegal drugs, especially opiates, are risk factors for developing conditions that might cause cerebral infarction. Owing to its conversion to morphine in the body, the opioid codeine, commonly included in prescription cough treatments, elevates the possibility of perinatal arterial stroke [45]. Together with the teratogenic effects of aspirin administered to animals in early gestation, a significant rate of embryonic death and resorption was noted when aspirin or other inhibitors of PG production were given to mice in later gestation [46]. nausea, vomiting, and dyspepsia are uncommon adverse effects seen by mothers on indomethacin. Any prostaglandin synthetase inhibitor, including indomethacin, has the potential to exacerbate gastritis and peptic ulcer disease. Moreover, it irritates the stomach to some degree (47).

2.7 Antidiabetic drugs

The majority of drugs taken during pregnancy cross the placenta, although it is unknown if they would have teratogenic effects on the growing fetus. It was discovered that while some anti-diabetic medications easily pass through the placenta, others do not. Pregnancy may cause teratogenic effects from medications that pass the placenta. One anti-diabetic medication that did not pass the placenta was gliburide. Thus, the safe use of glyburide during pregnancy has not had any adverse consequences on the fetus. Tolbutamide, glibenclamide, and glipizide, on the other hand, have easy placental passage. Pregnant women with diabetes mellitus are given their little doses [48–49]. About 70% of women with GDM will develop type 2 diabetes within ten years of giving birth. There are notable variations in the risk of type 2 diabetes among patients from different racial and geographic backgrounds, as per multiple studies [50]. Cohort studies were conducted on women with type 2 diabetes who were using biguanides (metformin 1.5-3g/day), sulfonylureas (glyburide 5–20 mg/day when prescribed), or both. Just two investigations discovered that the prevalence of congenital malformations was higher in women taking oral medications than in those receiving insulin [51]. The current study [52] looked at the negative effects of the diabetes drug metformin (MET) on Daniorerio embryonic development.Since metformin has a positive impact on a number of miscarriage risk factors associated with polycystic ovary syndrome, including obesity, hyperinsulinemic insulin resistance, and hyperandrogenemia, we hypothesized that treating hyperinsulinemic insulin resistance with the medication during pregnancy would reduce the rate of early pregnancy loss in women with the disorder. [53]

2.8 Antiarrhythmic drugs

Digoxin: For a very long time, pregnant women have used digoxin safely and effectively. Digoxin is neither teratogenic nor associated with any other unfavorable fetal outcomes when given at an appropriate dosage [54]. Medications belonging to the class 1 antiarrhythmic class function by blocking sodium channels. Research on procainamide, lidocaine, and quinidine showed that there are frequently no pregnancy-related side effects [55]. However, it has also been reported that class III antiarrhythmics can induce embryonic arrhythmia and transient cardiac arrest, which can result in severe hypoxia followed by reoxygenation of the embryo. Besides bradycardia, this is also present [56].It has also been shown that class III antiarrhythmics are proarrhythmogenic in animals.
An effective animal model for evaluating new medications' capacity to cause Torsade de Pointes is the rabbit. Because the rabbit heart seems to be particularly prone to Torsade de Pointes, the rabbit has shown to be a valuable animal model for evaluating novel medications' capacity to cause the syndrome [57].Nifedipine, carbamazepine, cyclophosphamide, prednisone, atenolol, and ibuprofen were among the medications used in prenatal care. Women who were subjected to calcium channel blockers believed they had a much higher chance of teratogenic effects [58]. Amiodarone is being used more often to treat supraventricular and ventricular arrhythmias. The high iodine concentration of amiodarone (75 mg per 200 mg) has limited its usage in pregnancy and raised concerns about possible effects on the developing foetus [59].

2.9 Antimalarials drugs

Pregnant women with malaria are one group of individuals for whom the riskbenefit relationship is frequently unclear. Consequently. Reluctant to prescribe during pregnancy, the doctor Pregnant women are advised not to take chloroquine or any other antimalarial medicine in certain regions where chemoprevention of malaria is strongly recommended [60, 61].Despite the embryotoxicity observed in laboratory animals, pregnant people taking artemisinin compounds, including a tiny amount in the first trimester, did not demonstrate increased risk for miscarriage, stillbirths, or deformity [62]. Several theories concerning the origins of DHA toxicity in developing embroys may be created based on research on malaria parasites. Pregnancy-related malaria is a serious public health concern and has significant clinical consequences for the mother [63]. The phathophysiology of malaria and the interactions between Plasmodium falciparum parasites and the placenta during pregnancy are intricate; almost all of these interactions favor the parasite at the expense of the mother and the fetus [64]. Compared to moderate doses of CQ exposure, which are usually used for comparable circumstances, high doses of CQ exposure during pregnancy have been more strongly associated with human birth malformations. Furthermore, Levy et al. (1991) found no evidence of congenital anomalies, but a higher than average rate of fetal loss [65].The teratogenic risk associated with taking birth control tablets right before or during the first few months of pregnancy has been linked to contradicting research. The only adverse effects on progeny linked to oral contraceptives are two types of congenital heart defects and congenital limb reduction [66, 67]. They affect the system that coagulates blood as well. For example, using oral contraceptives and becoming pregnant cause a decrease in the natural anticoagulant protein S levels [68]. Oral contraceptives are frequently coupled with other medications for exposure investigations and risk evaluations.
The current incompleteness of our understanding of the causes of birth abnormalities [69].

3.EFFECTS OF THERAPEUTIC DRUGS :-

◆ Thalidomide :-

Thalidomide was used in clinical settings during the 1960s. Malformations of the limbs decreased, esophageal and duodenal atresia, facial hemangiomas, urinary tract anomalies, veginal defects, dental abnormalities, ear anomalies, facial palsy, ophthalmoplegia, anophthalmia, microphthalmia, and coloboma were the outcomes. Tetralogy of Fallot was among them. The central servus system was not affected by rare incidences of cleft palate. The children were exceptionally bright. Human thalidomide birth defects could develop between 23 and 28 days after conception, with 14 days being the critical window. Prexial polydactyly, which results in six or seven toes per foot and ranges from triphalangeal thumb, was the most common anomaly seen in neonates delivered from about 20% of pregnancies exposed during this time.

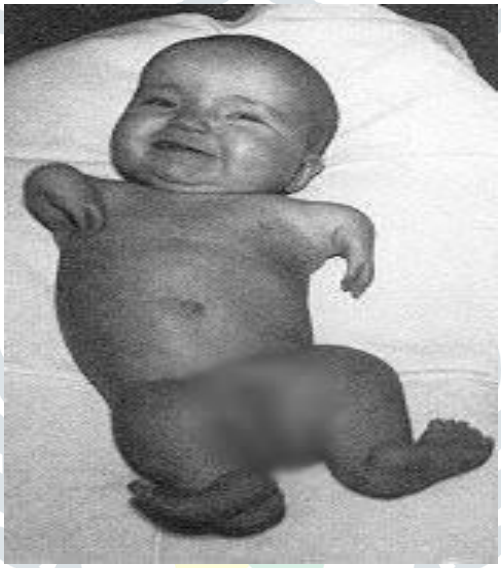

Fig 1: THALIDOMIDE EFFECT

McCredie suggested that disruption of neural crest-based sclerotomal organization was the pathogenetic basis of the limb abnormalities. McCredie and colleagues extended their studies of the visceral anomalies in infants who died with multiple congenital anomalies and longitudinal limb defects by attempting to determine whether neural crest injury would impair development of structures supplied by the sensory autonomic nerves derived from the injured zone of the neural crest. 89% of cases had a neuroatomic relationship when the autopsy data were applied to viscerotomal and sclerotomal maps. The authors proposed a developmental relationship within a multiple congenital abnormalities syndrome based on neurotomes et embryonic developmental fields with shared regional innervation. Thalidomide has an antiangiogenesis effect and is connected with teratogenicity. It also inhibits angiogenesis.

◆ Folic acid deficiency :-

Folic acid deficiency has been linked to neural tube abnormalities (NTDs) in many mothers who have given birth to children with NTDs; folic acid antagonists may also contribute to NTDs. It appears that folic acid deficiency is the cause of up to 70% of NTDs, particularly anencephaly. Food should be fortified with adequate folic acid, according to the US Food and Drug Administration (FDA). A daily dose of 0.4 mg of folic acid, commonly found

in over-the-counter multivitamin supplements, reduces the risk of non-transformed diseases (NTDs) by approximately 60% in the peri-conceptional stage. The US Public Health Service (PHS) recommends that all women in the US who are capable of becoming pregnant consume 0.4 mg of folic acid daily to reduce their risk of having a pregnancy affected by spina bifida or other NTDs. 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. Women who have once had an NTD are far more likely to have a subsequent affected pregnancy.

◆ Warfarin :-

Women with a history of mechanical heart valves or thromboembolic disease often require long-term anticoagulant medication. Infants who are exposed between eight and fourteen weeks of pregnancy have a 25% probability of being affected. Warfarin decreases the ability of proteins to bind calcium by preventing glutamyl residues from converting to carboxyglutamyl. Choanal stenosis may occur. The most common locations for calcific stippling are the paravertebral processes, proximal femurs, and tarsals. Tiny nails and brachydactyly are present in around half of affected infants; the upper limbs are more severely affected. Exposure during the first or second trimester of pregnancy may result in blindness, microphthalmia, and optic atrophy. ocular atrophy with microcephaly. Among the brain abnormalities are visual impairment, convulsions, hypotonia, and mental retardation. The skeletal defects, stippled calcification, and nasal hypoplasia observed in warfarin embryopathy may be attributed to proteins that prevent calcium binding during a critical ossification stage.

◆ Phenytoin :-

Phenytoin is a medication used to treat epilepsy. If the mother uses it in the first trimester, there's a small chance that the baby will be born with birth defects known as the fetal hydantoin syndrome. The pattern of abnormalities includes hypoplasia of the distal phalanges, dysmorphic craniofacial features, and developmental delay or obvious mental retardation. The incapacity of lymphocytes to metabolize phenytoin is linked to significant birth defects caused by the medicine. It seems that phenytoin fetal toxicity is inherited. In twins, the symptoms of the hydantoin syndrome have not always manifested simultaneously. There is a 1% to 11% chance that children exposed to phenytoin will experience developmental impairment. Chronic exposure is associated with a maximum 10% risk for the overall syndrome and a maximum 30% risk for individual defects.

3.1 Teratogen Sites of Action:

Teratogens have many more effects besides just directly harming the developing foetus, as was the case with thalidomide. Drugs may act on the foetus, the foetal placental unit, the mother, or the father, which may result in foetal abnormalities. These locations' activities fall into the following categories:

Fetus:

direct poisoning. Metabolites poisonous. harmful indirectly, such as anti-metabolites and anti-vitamins. pharmacodynamic effects, such as those on the heart. Changes in the equilibrium of endocrine systems Unit of foetal placental development: spinal cord, such as a spasm. Change in volume of amniotic fluid. Placental blood flow, either maternal or foetal. Nutrient transfer through the placenta, such as reduced active transport

Mother:

dietary modifications, such as vitamin or mineral shortages. biochemical alterations can have unintended consequences for the foetus, such as hyperglycemia. hormonal equilibrium.

Father: The sperm alters.

3.2 Teratogenic Defects in infants:

a) Spina Bifida:

This congenital abnormality occurs when the embryonic neural tube fails to close during the fourth week after fertilization, resulting in a divided spinal column (bifid). Myelomeningocele (MMC), also known as open spina bifida or spina bifida aperta, is the most common and severe variant. It is characterized by an open spinal cord that forms a placode on the back of the fetus or newborn baby, which commonly rests on a meningeal sac (formerly known as spina bifida cystica). Because they lack neural arches, the vertebrae at the level of the lesion are incomplete dorsally.

Pathogenesis and mechanisms:

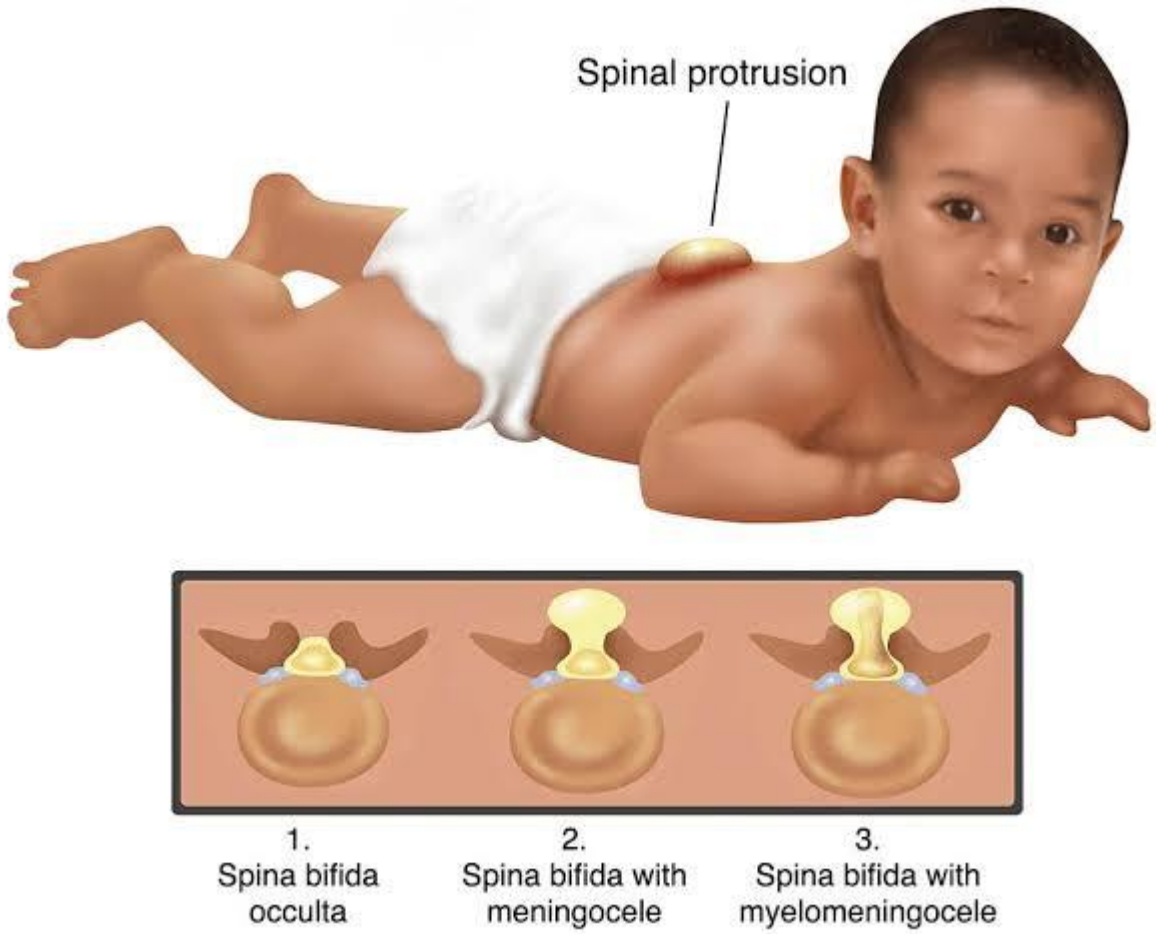

Fig 2 :- Spina Bifida

Failed neural tube closure in the embryonic spinal region, which results in an extended period of the open neural tube being exposed to the amniotic fluid environment, is the main pathophysiological abnormality in MMC. It is remarkable that even below the lesion level, the bifid neuroepithelium develops spinal motor and sensory function during an initial period of rather normal neuronal differentiation. But as the pregnancy goes on, the exposed spinal cord becomes hemorrhagic and the amniotic fluid's toxicity causes neurons to die. Function is lost when axonal connections are broken 21. Because of this, neurological impairment in MMC is frequently attributed to a "two-hit" process: neurodegeneration in utero and failed neural tube closure.

Treatment:

The severity of the condition determines how to treat spina bifida.The two main methods of treating spina bifida are surgery performed on the fetus during pregnancy or on the newborn following delivery. Before the 26th week of pregnancy, prenatal surgery is performed to treat spina bifida.

b) Hypocalvaria

The use of angiotensin receptor antagonists (arbs) or angiotensin converting enzyme inhibitors (arbi) during the second and third trimesters of pregnancy has been linked to a number of health problems, including prolonged patent ductus arteriosus, anuria, renal tubular dysplasia, limb contractures, and even prenatal death. These abnormalities are thought to be related to medication-induced fetal hypotension. We present a case with congenital calcaneovalgus foot, inferior vena cava (IVC) thrombosis, pneumonia, parenchymal illness, and skull ossification abnormalities in a newborn delivered to a hypertensive lady who continued to take arbs during her pregnancy.

Precautions: a lesser amount of exposure or avoidance of ACE inhibitor can avoid hypocalvaria.

c) **Alcohol spectrum disorders**.:-

Disorders related to fetal alcohol while pregnant can have a substantial impact on the development of the fetus, according to a large body of research on the long-term effects of prenatal alcohol exposure since alcohol was first identified as a teratogen in 1973. Fetal alcohol spectrum disorders are the aggregate term for the effects of alcohol on the body and brain. Serious illnesses like fetal alcohol syndrome (FAS) and its related conditions, such partial FAS (PFAS), require certain face abnormalities and other physical dysmorphology to be diagnosed.

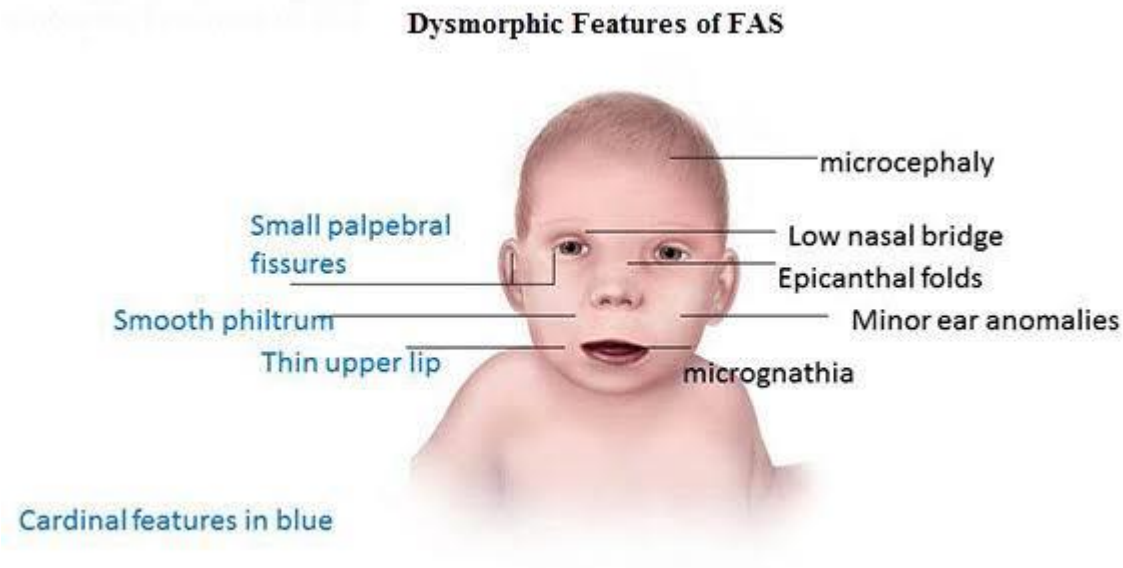

Fig 3:- Alcohol spectrum disorders

Precautions:

If a woman is pregnant or may become pregnant, she should abstain from alcohol in order to prevent FASDs. If a nwborn is not exposed to alcohol before birth, FASDs can be avoided.

d). dysmorphia:-

Body dysmorphic disorder (BDD), sometimes referred to as dysmorphophobia and dermatologic nondisease, affects 0.7% to 2.4% of the general population. It is a quite common disorder.Preoccupation with a perceived or minor flaw in one's physical appearance is the hallmark of the disorder. Alternatively, the person's concern is noticeably exaggerated if there is a little physical abnormality. Their obsession is linked to time-consuming rituals like staring into mirrors, continuously comparing their perceived ugliness to that of other people, or comparing different body parts. BDD patients have a skewed perception of their bodies, which may be linked to bullying or abuse in their early or teenage years.

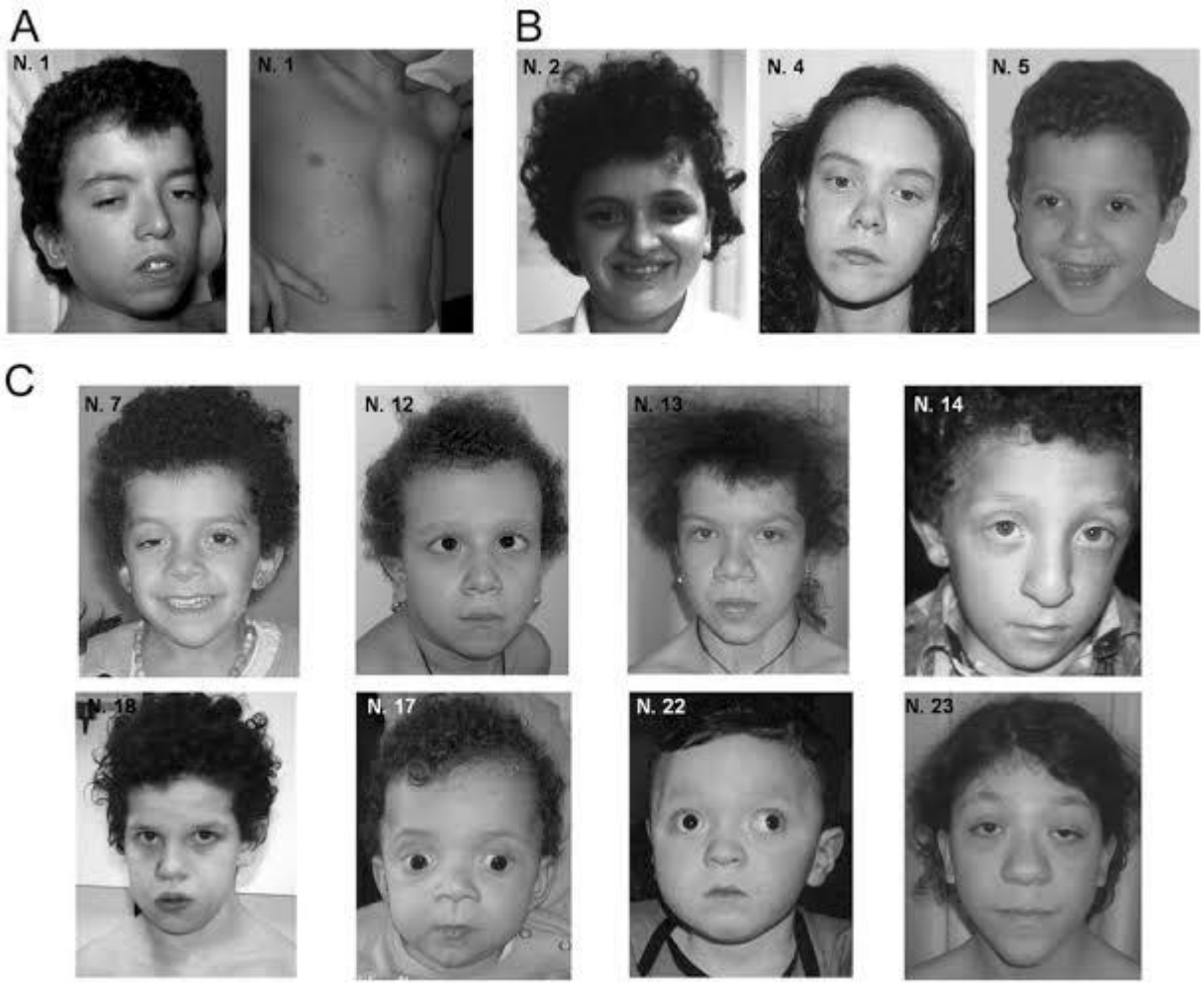

Fig 4 :- dysmorphia

Precautions:

Cosmetic surgery and dermatological treatment.1,2 The purpose of this review was to examine BDD's clinical characteristics, comorbidities, epidemiology, and available treatments in various clinical contexts.

e) *Clubfoot*:

Hippocrates introduced clubfoot, also known as Congenital talipesequinovarus (CTEV), approximately 300 B.C. He explained the differences between congenital and acquired clubfoot. The Latin words talus (ankle) and pes (foot); equinus (meaning "horse like"—the heel in plantar flexion) and varus (meaning inverted and adducted) are the origin of the term talipesequinovarus. Congenital talipesequinovarus affects 1-2 out of every 1,000 live newborns. It is among the most prevalent musculoskeletal birth malformations.

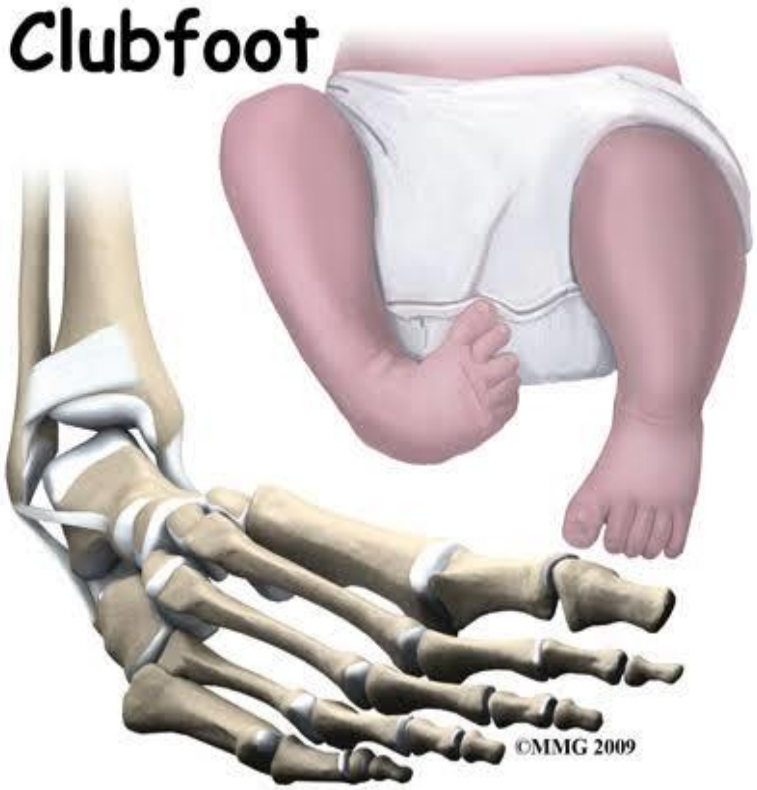

Fig 5 :- ***Clubfoot***:

Treatment:

A clubfoot develops during the second trimester of pregnancy from a normal developing foot. Clubfoot is not an anomaly of the embryo. Successfully treating clubfoot and comprehending its pathomechanics have long been

unresolved issues in contemporary medicine. Upon birth, clubfoot is typically identified just by examining the foot. Most orthopedic surgeons have agreed that the initial treatment

of a clubfoot should be nonsurgical and start as soon as feasible after birth.

Surgical Treatment of Clubfoot:

Surgery is necessary if the manipulation or serial casting treatment doesn't work. Usually, the child is not operated upon until they are between the ages of six and nine months. To treat clubfoot and realign the foot to its natural position, surgery is used. The surgical technique often entails the release and lengthening of the foot's joint capsule and taut tendons. A two- to three-hour surgical procedure includes a two-day hospital stay for observation. To repair the abnormality, surgery involved two incisions and the insertion of tiny pins. After four to six weeks of surgery, the pins are removed from the surgical foot, and a cast is applied for eighty-four days.

F) Cleft lip and palate :-

Cleft lip:

A cleft lip occurs when the front nasal and maxillary processes fail to fuse together, leaving a cleft that varies in size through the lip, alveolus, and nasal floor (a complete cleft indicates that there is no connection between the alarm base and the medial labial element, while an incomplete cleft does not extend through the nasal floor).

Cleft palate :

the cleft of the hard and/or soft palates caused by the inability of the palatal shelves of the maxillary processes to fuse. In the fourth developmental stage, clefts form. The precise locations of their appearance are dictated by the points in the embryo's existence where development was interfered with, which in turn affects the fusion of different face processes that did not occur.

Treatment:

Long-term Cleft Care: NAM, lip taping, genetic counselling, or SLP counselling for feeding 0–6 months: SLP and the primary clinician oversee eating and growth, a cleft surgeon repairs the lip deformity, and hearing evaluations and potential ventilation tube placements 9–12 months: fixing the palate and placing the ventilation tube 1-4 years: Thorough monitoring for language acquisition and dental assessment 4-6 years: Assessment for columellar lengthening/nasal tip correction, palate revision/speech surgery 4-6 years: Alveolar bone grafts, orthodontic intervention; > 12 years: Orthognathic surge and definitive rhinoplasty.

Fig 6 :- Cleft lip and palate

Drug use in pregnancy, FDA category:

FDA Rating	Condition
Category A	There is no risk in human research (pregnant women's studies have not shown any risk to the foetus during the first trimester).
Category B	Studies on animals have not shown any risk to the foetus; nevertheless, human studies are insufficient to make this determination.
Category C	One cannot rule out risk. Pregnant women have not had any trials that are satisfactory, but animal research have shown that there is a risk to the foetus; the drug's potential advantages may outweigh the risks.
Category D	Risk evidence (pregnancy-related research has indicated a risk to the foetus; possible advantages of the medication may exceed the risks).
Category X	Contraindicated (dangers to the foetus have been shown in trials involving pregnant

	women, and/or foetal abnormalities have been reported in investigations involving humans or animals; the risks of the medicine outweigh the potential benefits).

Table 1: Drug use in pregnancy, FDA category

- **List of safe and prohibited medications that have the potential to cause teratogenic effects.**

Sr. No	Safe Drugs (in pregnancy	Functions	Side effects (in fetus)
1)	Analgesic medications (Allopurinol, Indomethacin, Pethidine, and Paracetamol	Analgesic, antipyretic, used for kidney stones, gout, chronic arthritis, and connective tissue disease	No fetal abnormalities, Administered at the first stage of labor (6-8hrs) before delivery
2)	digestive aid (antiemetic, laxative, anti-diarrheal).	advantages for constipation, emesis prevention, and diarrhoea prevention.	No harmful or teratogenic effects During the first trimester, morning sickness treatment antispasmodic when expecting a child.
3)	anti-asthmatic medication (terbutaline, aminophylline, and ephedrine).	Chronic asthma, bronchial asthma, hay fever, and asthma.	Both teratogenic and no negative effects.
4)	Hydralazine, lidocaine, and methadone are antihypertensive agents.	Heart arrhythmia, hypertension, and congestive heart failure	Reduced foetal waste, increased birth weight and gestational age , and no negative consequences.
5)	Isoniazid, an antitubercular agent	treatment for tuberculosis infection.	No adverse effect.
6)	blood thinners (heparin	Anticoagulant action.	prevents harm to foetal brain.

Sr. No	Unsafe drug in pregnancy	Functions	Side effects (in fetus)
1)	Corticosteroids and cromolyn sodium as antiasthmatics	prevention for bronchial asthma.	causes malformation and retardation but has no teratogenic effect; it slows down foetal growth.
2)	gastrointestinal agent (cimetidine, ranitidine, cyclizine, hydroxyzine, prochlorperazine, sodium bicarbonate, antiemetics, cimetidine, hydroxyzine, prochlorperazine, H2 blockers).	Relieve from stomach acidity, Nausea and vomiting, Acid reducer.	adverse consequence, Poor results were displayed; frequent use needs to be discouraged.
3)	anti-microbial (sulphonamide, nitrofurantoin, and chlorphenicol).	Relief from UTI and typhoid	Hemolysis, bone marrow depression, and grey infant syndrome.
4)	agent antitubercular (Streptomycin).	Used in TB cases	Following placental passage, minor impact.
5)	Antihypertensive medications (captopril, diazoxide).	used as a vasodilator in hypertension.	Foetal harm caused by a drop in blood pressure.
6)	Ethacrynic acid is a diuretic.	Hypertension and edoema	Cut down on placental blood flow.
7)	cardiac medications (nifedipine, verapamil, a calcium antagonist)	Antihypertensive drug	Safe, although the foetus should need to be checked.
7)	Other medications (tetanus, vitamin D, calcium, and Pobenecid)	Antibiotics, control the salt balance	No negative outcome, given in the second or third trimester.

Table:- 2: A list of safe drugs during pregnancy.

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- **. Pregnancy-harmful medication list:**

Table : 3 A list of unsafe drugs during pregnancy.

- **list of contraindicated drugs during pregnancy**

Sir No	Contraindicated Drugs (in pregnancy)	Function	Side effects (in fetus)
1)	anticoagulants, like coumarin and warfarin.	Prevent coagulation.	Foetal mental impairment, congenital deformity, anomalies of the eyes
2)	Pain reliever (Colchicine's)	Used in Gout, arthritis	elevated chance of miscarriage and teratogenic impact.
3)	Agent that fights tuberculosis (Pyrazinamide, Ethinamide)	Treat TB case.	harmful effects and toxicity in the liver.
4)	Digestive aid (laxative: aspirin, dibasic sodium phosphate, castor oil)	stomach spasm and constipation.	Neonates are at high risk for malformation, tachycardia, urine retention, and hyperthermia.
5)	Agents that lower blood pressure (nitroprusside, serpine)	Treatment of chronic Hypertension.	cause the foetus to suffer from severe hypotension and die.
6)	Diuretics (Chlorthiazide)	Used in edema	thrombocytopenia and depression of the bone marrow.
7)	Antimicrobial (Tetracycline)	Used in mainly bacterial Infections.	calcium deposition or calcification of the bones of babies.
8)	Hypoglycemic drug used orally (Sulfonylurea)	Anti diabetic	Deformity and foetal demise
9)	Benzodiazepines (Chlordiazepoxide, Diazepam)	Sleep inducer	Cleft lips and heart and brain damage, as well as sadness among newborns.
10)	Anti-malarial drugs (Quinine)	Treatment of malaria	can result in early labour and abortion.

Table 4-: A list of contraindicated drugs during pregnancy.

4.LIST OF SOME DRUGS WHOSE USE IN CONTRAINDICATED DURING PREGNANCY :-

4.1 Alcohol :-

Introduction :-

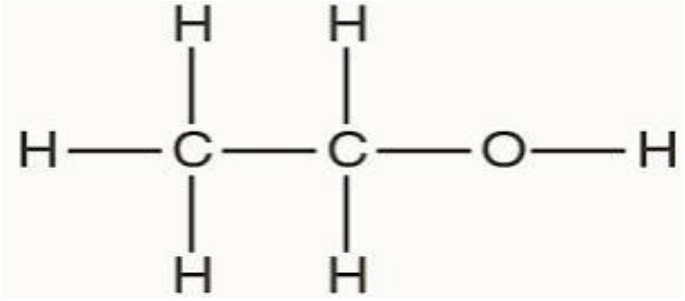
Prenatal alcohol exposure (AAE) can have detrimental consequences on a person's development and health that are both immediate and long-lasting. Alcohol is a hazardous chemical that can cause a variety of physical and neurological abnormalities in the developing baby. These abnormalities can result in long-lasting behavioral problems and other difficulties that may last the whole lifetime of the individual.[4] The recent focus of study has been to identify the pathways by which alcohol contributes to long-term health problems and vulnerability to diseases later in life, as well as to dissect the processes underpinning its immediate teratogenic impact on fetal development. Epidemiological research, controlled animal tests, and thorough laboratory testing have all confirmed that alcohol is teratogenic in humans. [5]

Mechanism of action

: In addition to interfering with brain development, the enzyme alcohol dehydrogenases (ADH) converts alcohol to acetaldehyde, which hinders DNA synthesis and amino acid transfer from the placenta to the baby. The susceptibility is correlated with ADH levels, which vary in expression as a result of genetic variances in ADH alleles.[6]

Teratogenic effect:

The teratogenic effect includes impaired intrauterine and postnatal growth, abnormal cognitive development, and a set of characteristics known as fetal alcohol syndrome (FAS), which includes low muscle tone, poor coordination, heart defects (ventricular and atrial septal defects), delayed speech, movement, and social skill development, and changes in facial appearance such as small palpebral fissures, large epicanthic folds, small head, small upper jaw, smooth philtrum, thin upper lip, etc. The primary cause of intellectual impairment is FAS. [7]



Structure No:- 1 (Ethanol) Alcohol

4.2 Thalidomide :-

Introduction :-

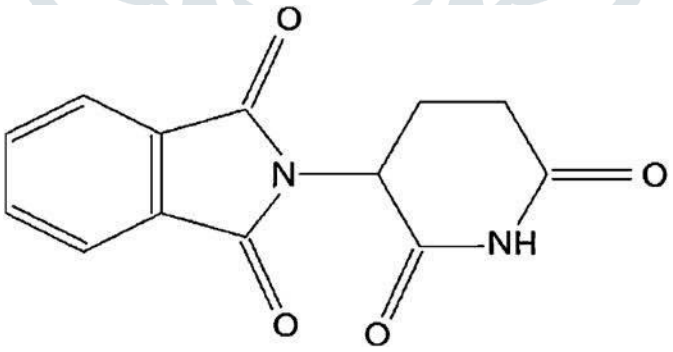
First of all, Thousands of children were born with severe birth defects as a result of the widespread use of thalidomide to relieve nausea in pregnant women in the late 1950s and early 1960s. People frequently reevaluate their medicine after finding out they are pregnant, however the product label for thalidomide cautions against using it during pregnancy. It is imperative to consult healthcare providers prior to making any prescription changes, even with potential hazards. They are able to balance the advantages of treatment with the dangers of untreated sickness during pregnancy. [8]

Mechanism of action :-

Renowned human teratogen thalidomide blocks angiogenesis by interfering with the IGF-1 and FGF-2 pathways. Through stimulating the transcription of integrin subunit B3 genes, it encourages root development and angiogenesis in limb buds. [9]

Teratogenic effect

Phocomelia, pre-axial polydactyl, and trifa langeal thumb are caused by exposure to trimethadide. face hemangiomas, abnormalities of the esophagus and duodenum, cardiac problems, renal agenesis, abnormalities of the urinary tract, sexual problems, dental anomalies, abnormalities of the car, facial palsy, ophthal moplegia, exophthal mia, and microphthal.[10]



Structure No:- 2 (Thalidomide)

4.3 Caffeine:-

Introduction :-

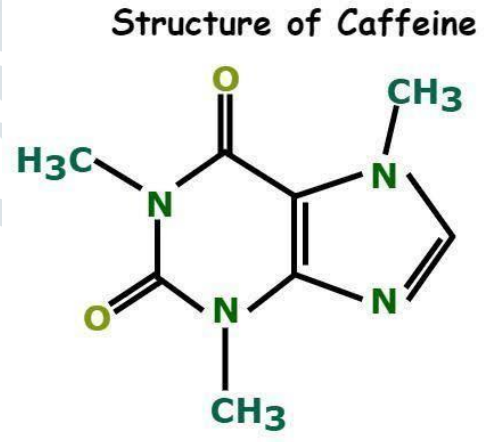
A chemical found in many foods and drinks, including coffee, tea, and crila, caffeine affects the nervous system and can cause restlessness and sleep problems. Nonetheless, consuming up to 200 mg daily is thought to be safe for women who are pregnant or nursing. Caffeine metabolism rate in the mother and her intake during pregnancy both affect how caffeine affects fetal development. Experts previously advised limiting a mother's daily caffeine intake to 300 mg. However, new EFSA rules recommend reassessment. [11]

Mechanism of action

One xanthine alkaloid that readily crosses the placenta and enters the fetal blood is caffeine. It releases catecholamines and increases motor activity by stimulating the central nervous system. both noradrenaline and adrenaline. Its diverse actions are further compounded by the fact that it inhibits phosphodiesterase activity and impacts serotonin turnover in particular locations

Teratogenic effect

Teratogenic substances abnormalities of the central nervous system, orofacial clefts, structural skeletal deformities, cardiovascular anomalies, adactyly, and thumb missing.[12]



Structure No:- 3 (Caffeine)

Conclusion :-

In conclusion, the teratogenic effects of various drugs during different stages of pregnancy highlight the critical importance of careful medication management for pregnant individuals. The timing of drug exposure plays a crucial role in the potential for congenital anomalies, with the first trimester often being the most sensitive period due to key developmental processes. Certain drugs, such as thalidomide and isotretinoin, have well-documented teratogenic effects, while others may pose risks that are less well understood. Healthcare providers must balance the benefits and risks of medication use during pregnancy, considering alternative treatments when possible. Preconception counseling and ongoing communication between healthcare providers and patients are essential to minimize risks. Further research is necessary to fully understand the teratogenic mechanisms of various drugs and to develop guidelines that ensure both maternal health and fetal safety. Ultimately, a cautious, informed approach is vital in safeguarding the health of both mother and child.

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 www.hon.ch/Dossier/MotherChild at

3))Ruedy.Early-pregnancy drug usage teratogenic risk.1984 Oct;30:2133-6 in Canadian Family Physician.PMCID:PMC2154342;PMID:21279129

2)Bonti M.,Sharabi S., and Addis A. Are System that categories the risks of drug use during pregnancy a creadiable source of information? Drug Safe, September 2000;23(3):245-53. PMID: 11005706; doi:10.2165/00002018-20002303000006.

3)Drugs.com: New FDA Pregnancy Categories Described.

4)Week-by-week Stages of Pregnancy: Foetal Development.

5)McCredie J. Embryonic neuropathy: a hypothesis of neural crest injury as the pathogenesis of congenital malformation.Med J Aust 1974;1:159-163

6) McCredie JM. Comments on “Proposed mechanism of action in thalidomide embryopathy.”Teratology 1990;41:239-242.

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

8)D’Amanto RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. PNAS USA 1994;91:4082-408

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

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

11) Afshar M, Moallem SA, HoushangMohammadpour A, Shiravi A,

MajidJalalian S, JafarGolalipour M. Teratogenic effects of carbamazepine on embryonic eye development in pregnant mice. Cutaneous and Ocular Toxicology.2010;29:10-5.

12)Tomson T, Battino D. Teratogenic effects of antiepileptic medications. Neurologic clinics. 2009;27:993-1002.

13) Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. The Lancet Neurology. 2012;11:803-13.

14) Tomson T, Battino D. Perucca E. Teratogenicity of antiepileptic drugs. Current Opinion in Neurology. 2019:32:246-52.

15) Hill DS, Włodarczyk BJ, Palacios AM, Finnell RH. Teratogenic effects of antiepileptic drugs. Expert review of neurotherapeutics. 2010;10:943-59. 16)Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Seizure 2008;17:166-71.

17) Norwitz R. Error, Greenberg A.
James, Antibiotics in Pregnancy: Are They Safe?. Reviews in Obstetricand Gynecology.Rev Obstet gynecol. 2009;2.135-6.

18) Czeizel AE, Rockenbauer M. Sorensen HT, Olsen J. use of cephalosporin's during pregnancy and in the presence of congenital abnormalities a populationbased, case control study. American Journal of obstetrics and gynecology 2001;184:1289-96.

19) Cross R. ling C. Day NP, McGready R, Paris DH Revisiting doxycycline is pregnancy and early childhood-time to rebuildits reputation? Expert opinion on drug safety. 2016;15:367-82.

20) Czeizel AE, Rockenbauer M. Teratogenic study of doxycycline. Obstetrics & Gynecology. 1997,89:524-8

21) Knothe H. Dette G.A. Antibiotics in Pregnancy: Toxicity and Teratogenicity, Infection, 1985; 13.

22) Czeizel AE, Rockenbauer M. Sørensen HT, Olsen J. A population-bused casecontrol teratologic study of ampicillin treatment during pregnancy. American journal of obstetrics and gynecology. 2001;185:140-7.

23) Andrew 1. Schafer, MD. (March1981) Teratogenic Effect of Antileukemic Chemotherapy. Arch inter med 1981,141:515.

24) Mikhali V.Blagoskionny, Teratogens As Anti-Cancer Drug, Cell cycle, 4:11, 1518-21.

25)Imran Ali, Waseem A. Wani, KishwarSaleem and

And Ashanul Haque, Thalidomide: A Banned Drug Resurged into Future Anticancer Drug. Current Drug Therapy. 2012:7:13-23.

26) Hyoun SC. Običan SG, Scialli AR. Teratogen update: methotrexate. Birth Defects Research Part A: Clinical and Molecular Teratology. 2012; 94:187-207.

27) Venerosi A, Valanzano A, Alleva E, Calamandrei G. Prenatal exposure to anti-HIV drugs neurobehavioral effects of zidovudine (AZT)+ lamivudine (3TC) treatment in mice. Teratoslogy. 2001:63-26-37.

28) Bailey H. Zash R, Rasi V, Thorne C. HIV treatment in pregnancy. The lancet HIV 2018;5:0457-67.

29) Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine
Association/Infectious Diseases Society of America.

30) Siu SS. Yeung JH, Pang MW, Chiu PY, Lau TK Placental transfer of zidovudine in firstt trimester of pregnancy. Obstetrics & Gynecology. 2005, 106:824-7.

31) MH Kaufman 1 the teratogenic effects of alcohol following exposure during pregnancy, und its influence on the chromosome constitution of the preovulatory egg 1997 Mar-Apr.

32) Keshav K. Gupta, Vinay K. Gupta, and Tomohiro Shirasaka an Update on Fetal Alcohol Syndrome Pathogenesis Risks. And Treatment August 2016.

33) Basil J. Zitelli MD, in Zitelli and Davis Atlas of Pediatric Physical Diagnosis, Genetic Disorders and Dysmorphic Conditions, 2018.

34) James H Kim 1. Anthony R. Scialli Thalidomide: the tragedy of birth defects and the effective treatment of disease 2011 Jul.

35) TD Stephens 1. CJ Bunde, BJ Fillmore Mechanism of action in thalidornide teratogenesis 2000 Jun.

36) Main teratogen categories and respective embryo-fetal effects during pregnancy (Scholl and Johnson 2000; Hernández Diaz et al., 2001).

37) Vadivel Ganapathy Drugs of abuse and human placenta2011 May23.

38) Structure No.1 (Alcohol)
Pw.live/exam/school/ethanol/formula.

39) Structure No.2 (Thalidomide)

reseaechgate.net/figure/molecular-structure of Thalidomide fig 1-241120639

40) Structure No.3 (Caffeine)
Geeksforgeeks,org/caffine-chemical-formula/

41) Niederhoff H, Zahradnik HP. Analgesics during pregnancy. Am J Med.
1983;75(5A):117-20.

42) DG. Aspirin in pregnancy: maternal and fetal effects. Pediatrics. 1978 Nov;62(5 Pt 2 suppl):930-7.

42.) Rudolph AM. Effects of aspirin and acetaminophen in pregnancy and in the newborn. Archives of internal medicine. 1981;141:358-63.

43.) Abou-Ghannam G, Usta IM, Nassar AH. Indomethacin in pregnancy: applicastions and safety. American journal of perinatology. 2012;29:175-86.

44.) Langer O. Oral antidiabetic drugs in pregnancy: the other alternative. Diabetes Spectrum. 2007;20(2):101-5.

45.) Ho FL. Liew C. Cunanan EC, Lee K. Oral hypoglycaemic agents for diabetes in pregnancy-an appraisal of the current evidence for oral anti-diabetic drug use in pregnancy. ANNALS-ACADEMY OF MEDICINE SINGAPORE
2007:36:672 49.

46) .obstetrics and gynecology 2007:50:959-71 50. Feig DS. Briggs GG, Koren

47). Oral antidiabetic agents in pregnancy and lactation: a paradigm shift". Annals of Pharmacotherapy. 2007:41:1174-80.

48) -Velázquez GA. Gómez-Oliván LM, Garcia- Medina S, Islas-Flores H. Hernández-Navarro MD, Galar-Martinez M. Antidiabetic drug metformin disrupts the embryogenesis in zebrafish through an oxidative stress mechanism.
Chemosphere. 2021:285:131213.

49) DJ, luorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2002:87:524-9.

50) chow, MD, Joseph Galvin, MRCPI, Brian McGovern, MD. Antiarrhythmic drug therapy in pregnancy, The American Journal of cardiology, vol 82 (20-10-1998)

51) Aruna MekalaPadmaja. Cardiac drugs in pregnancy,Indian journal of cardiovascular disease in women-WINCARS vol.3 No.2-3/2018

52) K, Sköld AC, WallinA, Danielsson BR. Teratogenicity of the class III antiarrhythmic drug almokalant. Role of hypoxia and reactive oxygen species. Reproductive Toxicology. 1999:13:93-101.

53) BR, Skold AC, Azarbayjani F. Class III antiarrhythmics and phenytoin: teratogenicity due to embryonic cardiac dysrhythmia and reoxygenation damage. Current pharmaceutical design, 2001;7:787- 802. 57. Magee LA, Schick B. Donnenfeld AE, Sage SR. Conover B. Cook L, McElhatton PR, Schmidt MA, Koren G. The safety of calcium channel blockers in human pregnancy: a prospective, multicenter cohort study. American journal of obstetrics and gynecology.1996;174:823-8

54)Robson DJ, Raj MJ, Storey GC, Holt DW. Use of amiodarone during pregnancy. Postgraduate Medical Journal. 1985:61:75-7.
55) WR, White NJ. Antimalarial drug toxicity. Drug safety. 2004;27:2561
56) MS. Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. Br Med J (Clin Res Ed). 1985;290(6480):1466-7.
57)Longo M, Zanoncelli S. Della Torre P. Rosa F, Giusti A. Colombo P. Brughera M. Mazué G, Olliaro P. Investigations of the effects of the antimalarial drug dihydroartemisinin (DHA) using the Frog Embryo.Teratogenesis by Assay-Xenopus (FETAX). Reproductive toxicology, 2008:25:433-41.
58) M. Zanoncelli S. Manera D. Brughera M. Colombo P. Lansen J. Mazué G. Gomes M. Taylor WR. Olliaro P. Effects of the antimalarial drug dihydroartemisinin (DHA) on tal embryos in vitro. Reproductive toxicology. 2006:21:83-93.

59) CJ, Edmonds S. Mutabingwa TK. Malaria in pregnancy, BJOG: An International Journal of Obstetrics & Gynaecology, 2005;112:1189-95.
60) JL., Harris C. Chloroquineembryotoxicity in the postimplantation rat conceptus in vitro. Teratology. 1993:48:213-26.
61) E. Saksela E, Saxén L. Teratogenic hazards of oral contraceptives analyzed in a national malformation register. American Journal of Obstetrics and Gynecology. 1981;140:521-4.
62) KJ, Louik C. Oral contraceptives and birth defects New England journal of medicine. 1978:299:522-4.
63) PC. Zacur HA. Contraceptive choices in women with coagulation disorders. American journal of obstetrics and gynecology. 1993;168:1990-3.
64) DT, PIPER JM, Glebatis DM. Oral contraceptives and birth defects. American Journal of Epidemiology. 1980;112:73-9.
65) JW, Zamah NM. Oral contraceptive side effects: where's the beef?. Contraception. 1995:52:327- 35.
66) A, Reddy TA, Bhavana K, Mutha S, Bakshi V. Assessment of Ocimum sanctum to normalize the estrous cycle in letrazole induced polycystic ovary syndrome in female Wistar rats. World J Pharm Res. 2018:7:907-19
67) McCredie JM. Comments on “Proposed mechanism of action in thalidomide embryopathy.”Teratology 1990;41:239-242
68) DJ, luorno MJ, Jakubowicz S, Roberts KA, Nestler JE. Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. The Journal of Clinical Endocrinology & Metabolism. 2002:87:524-9.
69) Robson DJ, Raj MJ, Storey GC, Holt DW. Use of amiodarone during pregnancy. Postgraduate Medical Journal. 1985:61:75-7.
70) Ho FL. Liew C. Cunanan EC, Lee K. Oral hypoglycaemic agents for diabetes in pregnancy-an appraisal of the current evidence for oral anti-diabetic drug use in pregnancy. ANNALS-ACADEMY OF MEDICINE SINGAPORE
2007:36:672 49.

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