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REVIEW ON "TERATOGENICITY"

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1. Abstract

Pregnancy is a special physiological condition where drug treatment presents a special concern because the physiology of pregnancy affects the pharmacokinetics of medications used and certain medications can reach the fetus and cause harm. Total avoidance of pharmacological treatment in pregnancy is not possible and may be dangerous because some women enter pregnancy with medical conditions that require ongoing and episodic treatment (e.g. asthma, epilepsy, hypertension). Also during pregnancy new medical problems can develop and old ones can be exacerbated (e.g. migraine, headache) requiring pharmacological therapy. The fact that certain drugs given during pregnancy may prove harmful to the unborn child is one of the classical problems in medical treatment. In 1960's pregnant ladies who ingested thalidomide gave birth to children with phocomalia. Various other examples of teratogenic effects of drugs are known. It has been documented that congenital abnormalities caused by human teratogenic drugs account for less than 1% of total congenital abnormalities. Hence in 1979, Food and Drug Administration developed a system that determines the teratogenic risk of drugs by considering the quality of data from animal and human studies. FDA classifies various drugs used in pregnancy into five categories, categories A, B, C, D and X. Category A is considered the safest category and category X is absolutely contraindicated in pregnancy. This provides therapeutic guidance for the clinician. This article focuses on various aspects relating to drug use during pregnancy.

Keywords: *Teratogen ,ionising radiation*

2. Introduction

Teratology is derived from the Greek noun teras, meaning monster, and historically has referred to the study of malformations early in life that result from exposure to chemicals such as mercury, lead, and other complex compounds. The original focus of this work was on gross physical malformations (and hence the borrowing of the Greek noun for monster), and more recently has referred to malformations that result from exposure to chemicals such as lead, mercury, or other compounds. In the period from the 1960s to 1980s, the concept was gradually extended to the domain of behavioural teratology, most clearly articulated by Riley and Voorhees. The key elements of this extension are twofold. First, the focus is on behavioural anomalies, rather than physical malformations. Second, and perhaps more far reaching, is an appreciation that many behavioural anomalies may be subtle in nature and not apparent at all stages of development. Closely aligned with the field of behavioural teratology is the field of toxicology. For the most part, behavioural teratology focuses on variations in behaviour that are associated with some known or suspected exposure to a potential toxin in utero.

3.HISTORY

Teratology was initially identified in the 1930s as a result of numerous pigs that were pregnant during the tests. Pigs were fed a diet deficient in vitamin A during these tests. All of those piglets eventually developed terrible abnormalities, with the primary loss of eyes.

The human rubella virus was discovered by Sir Norman Gregg in 1941 and was the first known human teratogene. As research advanced, experiments on animals using congeners of biologically prevalent compounds, most likely the amino acid analogue azaserine, were used to show the effects of xenobiotic agents on embryos. Aminopterin was used to end the pregnancy in the 1950s. Instead, after the medicine failed to cause the pregnancies to end, some handicapped children were born.art abnormalities and congenital cataracts were caused by prenatal exposure to this virus.

The main cause of encounter with teratogenic variations is a lack of public health care for pregnant women. Women who receive inadequate medical treatment are more likely to abuse alcohol and other drugs. The offspring of socially disadvantaged women are more susceptible to birth abnormalities because of these same general variables.

Conceptus development stage :

Depending on their gestational age, organisms exhibit different levels of susceptibility to exogenous stimuli. Up until the third week of gestation, a conceptus is a fertilised egg cell. The embryonic phase lasts from the third to the eighth week, and the foetal phase[5]. The critical phases of gestation are represented in Figure.2

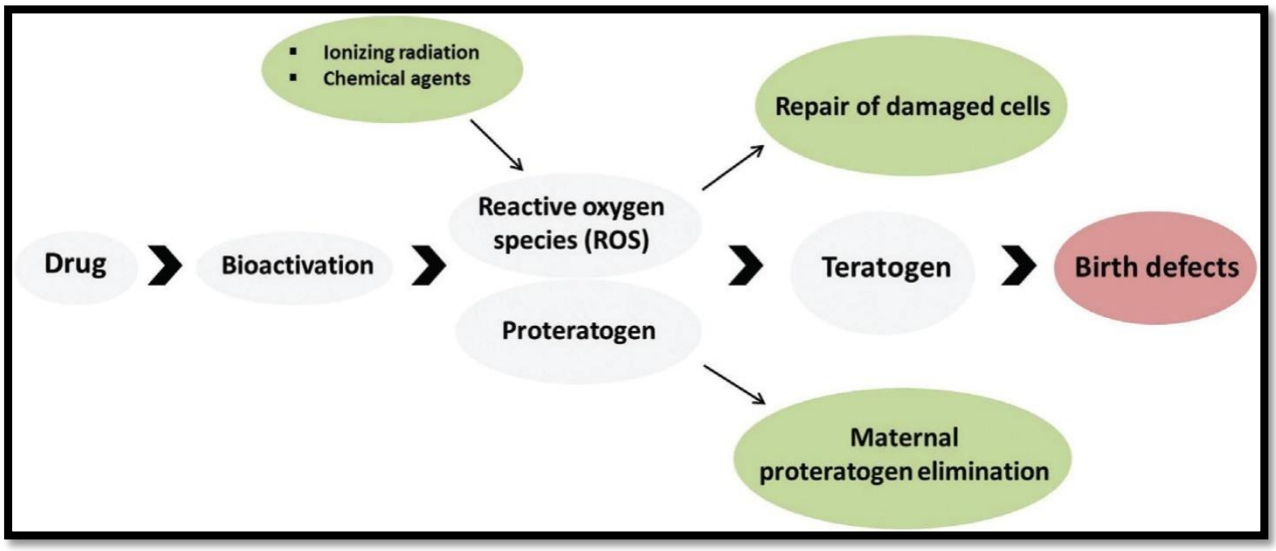


Figure 1: Teratogenesis pathways due to oxidative stress.

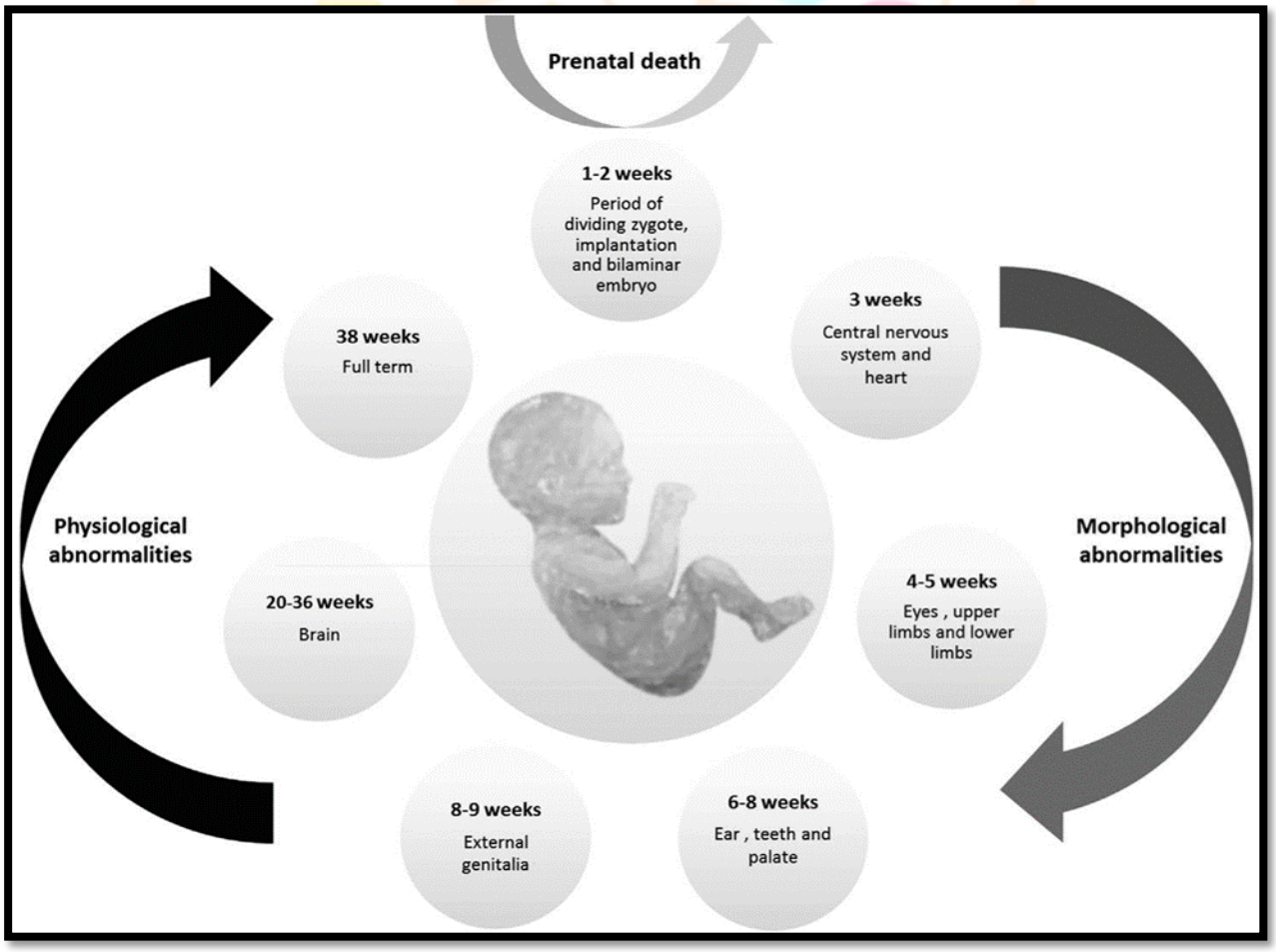


Figure 2. Critical stages of human embryological development

The first two weeks following fertilization are known as the "all-or-nothing" phase; if a contact with a teratogenic factor takes place, it can either result in spontaneous abortion or in a normal embryo-fetal development. Teratogenic exposure can cause significant phenotypic changes in the embryo, including changes to the central nervous system, limbs, and face, if it happens between the third and eighth weeks of gestation, when the majority of the morphological features develop. Some organs, like the brain and external genitalia, are still

developing after the ninth week of pregnancy, and exposure to teratogens can result in functional defects. However, from this phase forward, the majority of morphological traits are kept.

4. Natures of the agent

Depending on the teratogen's nature, teratogenic substances can have a variety of effects on the developing embryo. Physical teratogens, like ionising radiation, have an immediate impact on the developing embryo. Contrarily, before reaching the foetus, drugs and other chemicals are first digested by the mother's body. Different teratogenic susceptibilities can come from this metabolism's ability to either activate or inactivate pertinent metabolites.

General mode of action of teratogen :-

In defining the kind and scope of damage, the timing of the teratogenic insult in relation to foetal development is crucial. The three primary stages of mammalian foetal development are blastocyst formation, organogenesis, histogenesis, and functional maturation. Ethanol is one of the causes of teratogen which affects development at this very early stage. Many teratogens have the ability to inhibit cell division and kill embryo during cell division, which was involved in blastocyst formation. However, most of the time the embryo survives; its subsequent development does not usually seem to be compromised.

Gross deformities result from teratogen administration between Days 17 and 60 of organogenesis. The organisation of the embryo includes the eye and brain, skeleton and limbs, heart and main vessels, palate, and genitourinary system. The type of deformity caused by teratogen varies on the timing of exposure. For example, vitamin A derivatives (retinoids), which are important in morphogenesis and are strong teratogens, may have mutagenic consequences due to the poorly understood cellular processes of teratogens and teratogenic effects. Drugs like phenytoin and methotrexate affect the metabolism of folate but do not directly affect DNA.

During the latter phase of histogenesis and functional maturation, the development of the foetus is dependent on a sufficient supply of nutrients, and it is controlled by a number of hormones. At this stage, exposure to mutagens does not result in the development of gross structural deformities, but teratogens that disrupt the hormonal environment or the availability of nutrients can negatively affect the development of the organism. The masculinization of female foetuses exposed to androgens is possible. In the 1950s, stilbestrol was frequently administered to expectant mothers with a history of recurrent miscarriage (for questionable reasons). It causes dysplasia of the infant's vagina and a higher incidence of vaginal cancer in women in their teens and twenties.

5. Drugs and Birth Defects:-

The clinical consequences of drug teratogens must be placed in the overall context of developmental defects in humans. Defects may be from genetic, environmental, or unknown causes. Approximately 25% are known to be genetic in origin (e.g. Mendelian. chromosomal). Approximately 65% of defects are of ostensibly unknown but probably reflect combinations of genetic and environmental factors .The risk for malformation after exposure to a drug must be compared with the background rate, which for major malformations in the general population usually is cited as 2-3%. A major malformation is defined as one that is incompatible with survival, such as anencephaly; or one requiring major surgery for correction, such as cleft palate or congenital heart disease; or one producing major dysfunction (e.g., mental retardation). If minor malformations also are included, for example car

tags or extra digits, the rate may be as high as 7-10%. Drug exposure accounts for, at most, 2-3% of birth defects .Potentially almost any drug used by the mother during pregnancy could be deleterious to the foetus, causing an anatomic defect (teratogenic). Almost all lipid-soluble compounds readily cross the placenta. Water-soluble substances pass more easily when of lower molecular weight. The degree to which a drug is bound to plasma protein also influences the amount of drug that is free to cross the placenta. Overall, most drugs cross the placenta to some degree, with the exception of large organic ions such as heparin (both fractionated and unfractionated) and insulin .

1. **Mechanism of drug interaction:**

i. . Pharmacokinetic

ii. . Pharmacodynamic

I. Pharmacokinetic Interaction:

These Interactions alter the concentration of the object drag at site of affecting its absorption, distribution, metabolism, or excretion.

i. Absorption:

- Drug absorption is the movement of drug from side of administration into the systemic circulation drug absorption is commonly character bioavailability. the fraction or percentage of active dig medication that routes the systematic circulation intact by any route drug that are administered intravascularly a 100 % bioavailable since they are delivered directly into the bloodstream.
- Can be minimized by administered two drugs with a gap of 2-3 hours
- E.g. Tetracycline and calcium/ ion salts
- Nausea and vomiting in early pregnancy may decreases the amount of drug available for absorption
- Gastric acid production is also decreased during pregnancy, whereas mucus secretion is increased, leading to an increase it gastric PH.

ii. Distribution:

- Distribution describes the reversible transfer of a drug between different location following its entry into the systemic circulation. The volume of distribution is used to indicate how extensively, a systemic dose of medication is ultimately dispersed throughout the body.
- Due to displacement of one drug from its binding sites on plasma protein by another drug .
- E.g. Quinidine und Digoxin

iii. Metabolism:

- Drug metabolism involves chemical modifications of a drug through specialized enzymatic systems. For some medications, administered as inactive pro- drug , metabolism leads to loss of drug activity. The liver accounts for the metabolism of a vast majority of drug
- Certain drug reduces or enhance the rate of metabolism of other drugs.
- E.g. Microsomal enzyme inducers like barbiturate, rifampicin can cause contraceptive failure.

iv. Excretion:

- Renal drug excretion depends on GFR, tubular secretion, and reabsorption GER is 50% higher by the first

trimester and continues to increase until the last week of pregnancy. If a drug slowly excreted by glomerular filtration, its renal clearance is expected to parallel changes in GFR during pregnancy. For example, cefazolin and clindamycin exhibit increased renal elimination during pregnancy.

- Despite a uniform increase in GFR during pregnancy, differences in renal tubular transport can result in differing effects on renally cleared drugs.
- Important in case of drugs actively secreted by tubular transport mechanism.
- E.g., Probenecid inhibits tubular secretion of penicillin and cephalosporin and prolong their plasma t1/2 .

2 .Pharmacodynamic Interaction:

- These interactions are due to modification of action of one drug at the target site by another drug independent of changes in its concentration.

This results in....

- Enhanced response - synergism
- Attenuated response - Antagonism
- Abnormal response- Pharmacodynamic interaction are those in which drugs influence each other's effects directly. Often, however, a Pharmacodynamic interaction is actually desired, if mutually potentiating effects in the same direction are aimed at, E.g. In the use of anti-infective or in pain therapy.
- Pharmacodynamic is affected by receptor binding and sensitivity, post receptor effects and chemical interactions.
- Additivity- Two drugs act on the same receptor and the combine effect is the sum of the two drug up to the maximum effect.
- Potentiation- Types of synergism in which one drug has no effect but can increase the effect of the other drug .

6. Common human teratogens :-

- **Drugs :-**
  - ACE inhibitors:-benazepril, enalapril, captopril
  - Acid nonsteroidal anti-inflammatory agent:-diclofenac
  - Androgen hormones:-oestrogen
  - Antiepileptics:-phenytoin, valproic acid, carbamazepine, trimethadione
  - Antineoplastic:-folic acid
  - Antagonists:-methotrexate, amiopterine
  - Retinoids:-isotretinoin Penicillamine Thalidomide Warfarin Xanthine
  - Alcoloids:-caffeine
- **Pesticides:**-organophosphates
- **Herbicides:**-glyphosate Sulfur mustard
- **Unnecessary chemicals**:- Alcohol, Cocaine
- **Other chemicals**:- Methyl mercury
- **Physical agents**:- Cigarette smoke

- **Ionising radiations**:-high doses at least >5 rad
- **Biological agents (embryo fetal infections)** :-Rubella Cytomegalovirus
- **Maternal diseases:-** Diabetes ID, epilepsy
- **phytochemicals**:- Veratrum alkaloid cyclopamine
- **Miscellaneous agents**:- Lambda carrageenan

Fig :- common human teratogens

- **Drugs:-**

i. Penicillamine:

A sulfhydryl-containing amino acid called D-penicillamine (DPA) (dimethylcysteine) has the ability to chelate metals, notably copper, and speed up their rate of elimination in the urine. Increased dosage results in a decrease in tissue copper concentration. Numerous investigations have shown that pregnant women who received DPA displayed foetal abnormalities. Copper may play a mediating role in the manifestation of prenatal abnormalities, according to a link between low copper levels and a high prevalence of congenital deformities and death.

DPA has the capacity to pass the placental barrier, which may account for its teratogenic potential. DPA treatment during pregnancy resulted in babies with significant connective tissue abnormalities. It is the preferred treatment for conditions including cystinuria, rheumatoid arthritis, and Wilson's disease, all of which are known to have severe teratogenic consequences in pregnant patients. Elastic and collagen fibres in the dermis must be cross-linked in order for this to happen. This enzyme, lysyl oxidase, is copper dependent. Unusual elastic fibre buildup results from the indirect suppression of enzyme activity caused by the removal of copper from tissues by penicillamine.

Additionally, the drug's suppression of lysine residue deamination is required for elastin and collagen maturation, which contributes to the aberrant accumulation of elastic fibres.

ii. Thalidomide:-

The worst known teratogen in the history of medicine is thalidomide. Even extremely small amounts of thalidomide consumption cause severe limb abnormalities in the developing fetus.

Phocomelia and amelia, which are characterised by severe shortening or entire disappearance of legs and/or arms, are limb abnormalities brought on by thalidomide, whereas anotia, microtia, and hearing loss are ear malformations.

Through abnormal nuclear Factor-kB activity, thalidomide has the ability to cause reactive oxygen species and oxidative stress, which upregulate the production of bone morphogenic proteins. This modification blocks signalling proteins, protein kinase B, and fibroblast growth factor (Fgf8/Fgf10) pathways that are known to be crucial for cell survival and proliferation. Organ dysgenesis is brought on by thalidomide use in the first trimester of pregnancy.

The embryonic body's long bone growth is slowed by thalidomide's antiangiogenic impact, which also causes cell death and downregulation of growth factors like Fgf8 or Fgf10. One of the causes of cell death is the disruption of the signalling pathways for growth factors. Mesenchymal loss and limb abnormalities are the results of this chain of events[25,27]. It produces free radicals that harm the cellular macromolecules of developing organisms and have teratogenic effects.

Thalidomide was discovered to produce reactive oxygen species in rabbits, damage DNA, and accumulate 8-hydroxy20-deoxyguanosine. Cereblon, a protein that binds to thalidomide, has just been discovered. The main target of thalidomide teratogenicity, cereblon, is bound by the drug and its activity is reduced.

iii. Warfarin:-

It is an effective natural coumarin that functions as a rodenticide and causes internal bleeding in rats and mice. Additionally, clinical medicine has accepted it. Warfarin has the benefits of being water soluble, oral bioavailable, and reversible with vitamin administration[25].

Fetal malformations with warfarin are linked

During the first six to nine weeks of pregnancy, it causes embryo toxicity. Warfarin medication during pregnancy has been linked to anomalies of the CNS, eye, jaw, and urinary system in addition to spontaneous abortion, stillbirth, nasal hypoplasia, stippled epiphyses, distal limb hypoplasia, and distal limb hypoplasia. The primary causes of CNS malformations and neurological abnormalities in children and adults born to women are microhemorrhages in neuronal tissue brought on by inadequate vitamin K reserves and low levels of vitamin K dependent procoagulant factors in the foetus.

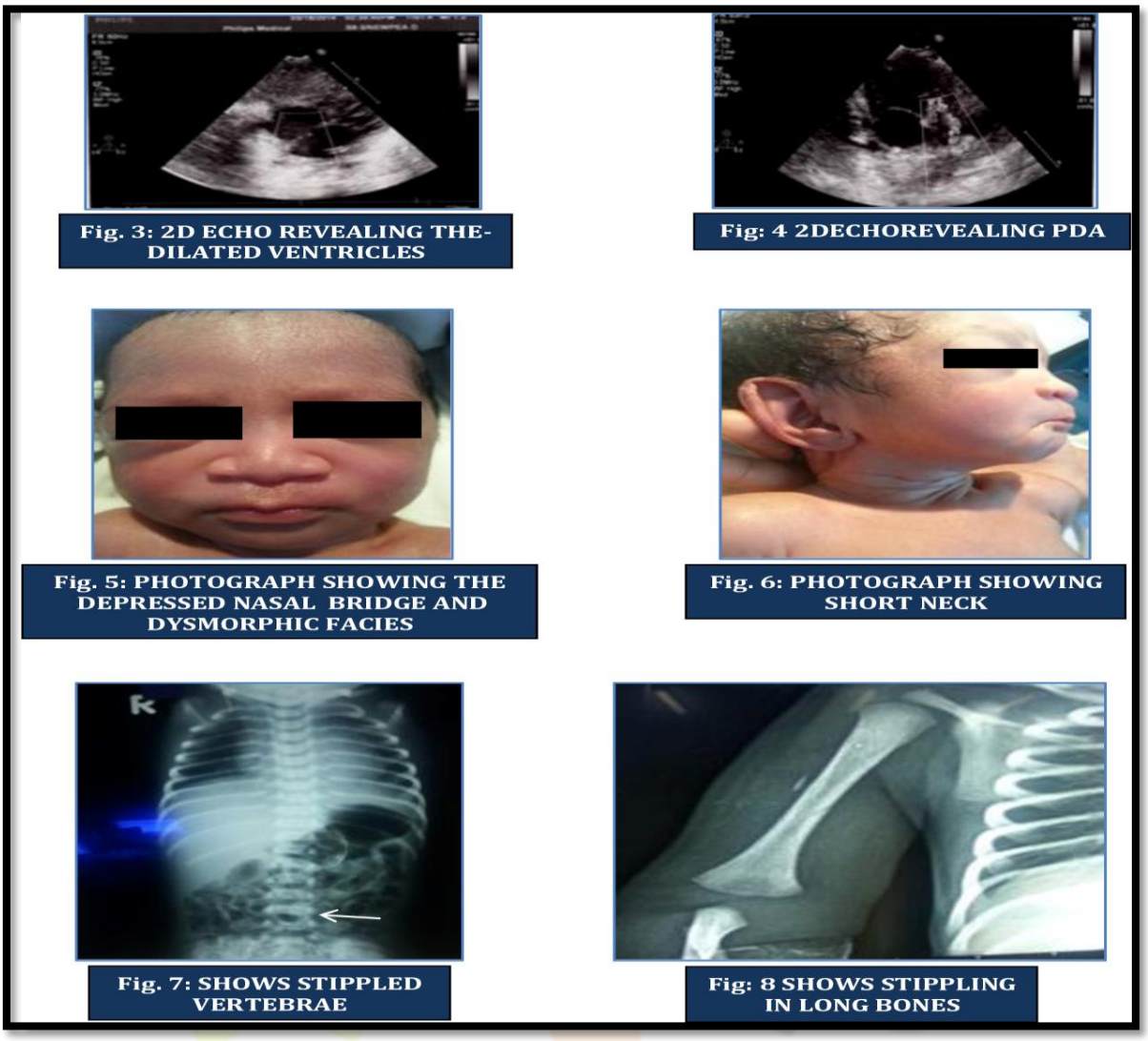


Fig:-Fetal Warfarin Syndrome

- **Unnecessary chemicals:-**

i. Alcohol:-

Fetal alcohol syndrome (FAS) was first recognised and published in a study report on the teratogenic consequences of alcohol in 1973. FAS describes a pattern of birth abnormalities in offspring of habitual drinkers. Children with FAS typically have abnormalities of the brain, craniofacial structure, and limbs, as well as a high risk of developmental delays. Alcohol teratogenicity was primarily seen in the kids of pregnant women who drank a lot of alcohol. The foetal vulnerability to alcohol harm can be influenced by a number of variables, such as genetic traits inherited from the mother or father. Alcohol drinking by the father is thought to have the potential to change the genetic makeup passed down to the foetus and add another source of variability and severity in FAS.

Alcohol can easily pass the placental barrier. The major cause of FAS is the ability of alcohol and/or one or more of its metabolites, such as acetaldehyde, to cross the placenta. Alcohol builds up in amniotic fluid, which serves as a reservoir for unaltered alcohol and acetaldehyde due to the kinetics of amniotic fluid circulation and the lack or very low levels of the enzymes needed for drug biotransformation during foetal development. As a result, both substances are exposed to the embryo foetus long after they have left the mother's body.

Fig:- Alcohol consumption in pregnancy

I. Cocaine :-

One of the most potent psychoactive substances is cocaine. It has the capacity to impede sodium ion permeability and prevent the post-synaptic re-uptake of catecholamines, dopamine, and tryptophan, producing an anaesthetic effect.

Metabolites with potent pharmacologic actions and neurotoxic properties include benzoylecgonine and benzoylnorecgonine. The drug's and its metabolites' capacity to pass the placental barrier is what causes the very damaging effects on embryonic development. Cocaine has an indirect impact on foetal development due to its effects on the maternal cardiovascular and autonomic systems.

The efficient operation of the vascular system is necessary for the foetus to get an appropriate amount of nutrients and for the clearance of metabolic waste. These prerequisites affect both the morphological changes that occur during organogenesis and the development of the embryonic vascular system.

When cocaine is introduced during the first trimester, its strong vasoconstrictive effects may raise the likelihood of structural abnormalities. The cocaine-treated women displayed placental abruption, which is one of the major causes of maternal morbidity and foetal mortality. Placental abruption is the early separation of a normally implanted placenta. This result could be a result of the medication-induced maternal hypertension. Cocaine administration to pregnant ewes results in a dose-dependent acute decrease in uterine blood flow, which lowers foetal arterial oxygen partial pressure and oxygen content and causes the foetal body's tissues to be destroyed and organ deformity. Due to the concomitant foetal hypoxemia and the generation of foetalcatecholamines, cocaine exposure enhances the cardiovascular effects on foetuses, such as heart rate and mean arterial pressure.

- **Other chemicals:-**

i. Methylmercury:-

Methylmercury is well-known for having a range of toxicities, including those of a neurotoxic, an endocrine disruptor, and a teratogen. Both humans and wildlife experience changes in behaviour and health as a result of exposure to methylmercury.

Exposure is frequently caused by eating methylmercury-contaminated food, such as fish. Humans exposed to

high concentrations of chemicals during pregnancy experience neurobehavioral consequences such cerebral palsy and severe mental impairment. Additionally, it is linked to early sensorimotor impairment, such as a delayed initiation of walking, and lower birth weight. Neurobehavioral alterations were seen in exposure studies on rats and nonhuman primates. Additionally, it has neurotoxic effects on the development of the foetus and child. Pregnant women and women who are close to becoming mothers are advised to avoid exposure to methylmercury to avoid these teratogenic effexposures.

ii. Lead acetate:-

Lead is a widespread issue in occupational and public health that has a number of negative impacts on both men and women. An earlier experimentation investigation showed lead nephrotoxicity. Both male and female reproductive systems are impacted by high dosage exposure.

In women exposed to lead, the frequency of miscarriages and stillbirths rises. Increased prevalence of menstruation irregularities, spontaneous abortions, and threatening abortions are serious impacts of lead exposure. The growth and maturation of the ovarian follicles in mice was found to be stopped by the oral administration of lead acetate. Additionally, it has harmful effects on sperm in male progeny mice, causing aberrant spermatozoa morphology. As a result of it disrupting the sertoli cells' metabolic activity, it has the impact of causing abnormalities in the stages of spermatogenesis and spermiogenesis.

- **Physical agents:-**

Cigarette smoking:-

One of the main causes of general developmental problems is maternal cigarette smoking. The foetus' growth rate has decreased. various substances, including nicotine, Smoking causes the emission of cyanide and carbon monoxide, which prevent amino acids from travelling across the placenta. The precise mechanism causing teratogenic consequences in humans is unknown, however several processes have been hypothesised, including placental necrosis, obstruction of placental exchange, and activation of metabolic enzyme-based hazardous reactive metabolites.

Smoking-related carbon monoxide crosses the placenta and raises blood levels of carboxyhemoglobin, which has a longer half-life in foetal blood than in maternal blood.

Because of the decreased perfusion of embryonic tissues caused by nicotine's vasoconstriction action, uterine vascular constriction and intrauterine growth retardation ensue. Furthermore, it raises the danger of perinatal morbidity and mortality. Preterm delivery, premature birth, intrauterine growth retardation, perinatal mortality, subfertility, abnormal placentation, childhood morbidity and mortality, congenital malformations, gastroschisis, cardiac defects, chromosomal anomalies, and central nervous system defects are all linked to perinatal mortality.

Fig:-nicotine affect in pregnancy

- **Maternal diseases:-**

Diabetes:-

The main cause of perinatal mortality in these infants is congenital abnormalities, which are more likely in the offspring of insulin-dependent diabetic moms.

These impacts' underlying processes are not well known. Diabetes' metabolic changes cause an increase in the synthesis of components of the basement membrane, which are crucial to morphogenesis. Maternal diabetes selectively modifies gene expression in the growing rat embryo, according to a previous study in rats, and the modifications involve molecules (extracellular matrix components) that are crucial for morphogenesis .Additionally, alterations in mRNA and related proteins were detected. In the embryos of diabetic rats, altered protein kinase C isoform activity and distribution were seen. When hypoglycemia is present in the early stages of organogenesis, rats experience teratogenic consequences.

7. FDA Categories for drug use in pregnancy:-

The food and drug administration are responsible for protecting the public health by ensuring the safety ,efficacy, and security of human and veterinary drugs biological products and medical devices and by ensuring the safety of our nations food supply, cosmetics and product that emit radiation.

In1979, the food and drug administration developed a system determining the teratogenic risk of drugs by considering the quality of data from animal and human studies. It provides therapeutic guidance for the clinician. Category A is considered the safest category but some drugs from categories B, C and D are also used in pregnancy. Category X is the only rating that denotes a drug is absolutely contraindicated for use during pregnancy. some of the drugs commonly used during pregnancy and their categories (as peer FDA categorization)are mentioned in the table given below:

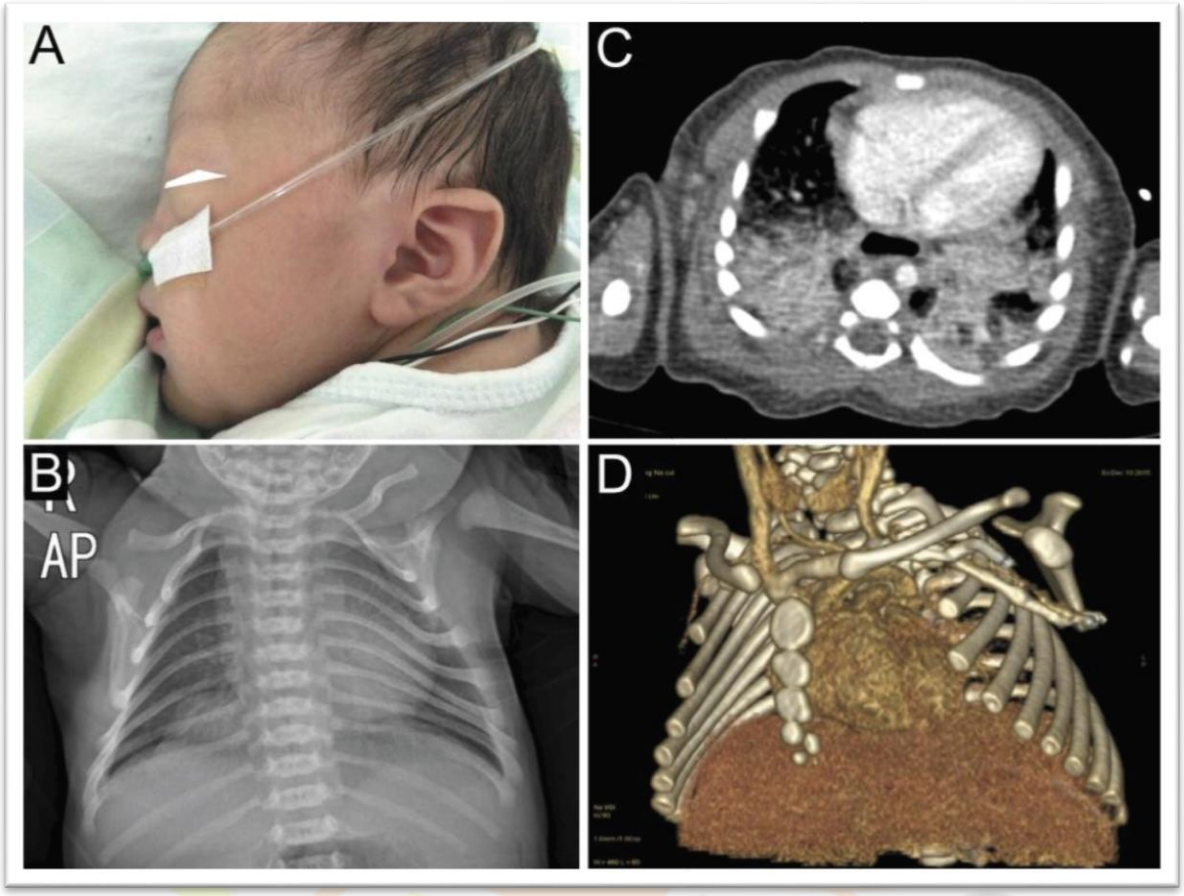
Drugs	Category
Analgesics and Antipyretics	B and C
Acetaminophen	B
Phenacetin	B
Aspirin	C
Antiemetics	B and C
Doxylamine	B
Meclizine	B
Cyclizing	B
Dimenhydrinate	B
Antibiotics	B and C , D
Penicillin, ampicillin, Amoxycillin	B
Cloxacillin, cephalosporin	B
Erythromycin	B
Gentamicin	C
Amikacin	C/D
Streptomycin	D
Sulphonamides	B/D
Tetracycline's	B
Amoebicides	B
Anthelmentics	B
Antimalarials	C
Antifungals	C
Anti TB Drugs	B and C

Ethambutol	B
INH	C
Rifampicin	C
Pyrazinamide	C
PAS	C
Vit. B, C, D, E, folic acid	A
Thyroxin	A
Androgens	X
Oestrogens	X
Progestogens-Hydroxyprogesterone	D
Medroxyprogesterone	D
Norethindrone	X
Bronchodilators	X
Norgestrel	C

8. Case Report

A 19-year-old patient, gravida 1 para 0, was referred foramenorrhea for 7 weeks 6 days. The patient had beendiagnosed with CML 1 year earlier and had been taking200 mg radotinib twice daily orally for 1 year. Six months before referral, in chronic phase, a complete cytogenic responsewas achieved. Normally, the patient had regular menstruation.The result of urine human chorionic gonadotropin (HCG) testwas positive and the ultrasound examination showed that Gsac was 1.26 cm. The fetal pole measured 2.4 mm (5 weeks 5days of gestation). Fetal heart beat was 105 bpm/min. She wasconcerned about the teratogenic effect of radotinib; hence shedecided to have a termination of pregnancy.The patient visited the hospital again 3 years later at 22years old for 11 weeks and 4 days of amenorrhea. Usuallyshe had regular menstruation. The patient had been taking300 mg of radotinib twice daily orally at that time but hadstopped taking radotinib after a urine HCG test wasconfirmed to be positive 12 days prior to this consultation.Ultrasound examination revealed a single intrauterinepregnancy of 12 weeks and 3 days of gestation. It wasconjecturable that she had taken radotinib until 10 weeks and5 days of gestation. The patient chose to continue thepregnancy and stopped taking radotinib. Blood analysisrevealed the following: white blood cell count of 5,490cells/mm3, hemoglobin level of 9.4 g/dl, and platelet countof 64,000 cells/mm3. Her renal and liver functions werenormal. The pregnant woman had regular antenatalcheckups; there was nothing significant to report. She had acomplete blood count every month. There

was no medical opinion of CML deterioration.



At the 39th week and 6th day, the patient gave birth to a baby girl (3.330 kg) vaginally. The Apgar score of the infant was 8 at 1 min and 9 at 5 min. Examination revealed both low-set ears and absence of angle between the forehead and nose (Figure 1A). No other external deformation was found. However, while the patient was breastfeeding, cyanosis and around 70% of desaturation occurred in addition to cow-like crying of the infant. Chest x-ray revealed haziness on both lower lungs. Rib deformity was suspected (Figure 1B). Chest computed tomography showed atelectasis on both lower lungs (Figure 1C). The rib cage was found to be normal (Figure1D). On echocardiogram, there was nothing significant toreport. Laryngoscopy revealed laryngomalacia. The epiglottiswas omega-shaped and arytenoid collapsed duringinspiration. On placental pathological examination, there wasincreased intervillous fibrin deposition without any otherabnormal findings. The infant's desaturation and atelectasishad improved by the time she was 10 days old. Therefore, shewas released from the hospital. There were no other abnormalfindings during the 3-month follow-up visit.

Conclusion:-We witnessed teratogenic effect of radotinib , hence the first pregnancy was prescribed for women of chid bearing age through education about contraception is necessary.

6. Conclusion:

- Understanding the mechanism of the Induction of birth Defect Is Key to determine How to prevent these effects
- Further increasing the accuracy of experimental animal extrapolation will aid in the interpretation of experimental data in order to more accurately determine the risk of a given compound to elicit birth defects in humans

- Choose the appropriate drug, avoid unnecessary exposure.
- Educate patient before starting the treatment.
- Risk benefit analysis

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