

TERATOGENIC EFFECT OF VARIOUS DRUGS ON PREGNANCY: A REVIEW

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Abstract— It is said that people get a chance to live their childhood again when they become parents. They see the world through their child's eyes but what if the child is born with disabilities or certain disorders? Will their parenthood be so easy, no and this present article focuses on certain drugs that shows teratogenic effect which can hamper child's growth and even lead to miscarriage. Few drugs like thalidomide, valproic acid, phenytoin, corticosteroids, mycophenolate, methotrexate and some social drugs are discussed with their hazardous effect on developing fetus.

Index Terms— Disabilities, Teratogenic, Miscarriage, Hazardous, Fetus.

I. INTRODUCTION:

In pregnancy, drug treatment has threat of potential teratogenic effect. The physiology of pregnancy affects the pharmacokinetics of medication. Some medication can reach to the fetus and cause harm [1].

Drug play important role in improving human health and promoting well-being. However, to produce the desired effect they have to be safe, efficacious and have to be used rationally [2].

The teratogenic effect of drug affects the fetus depends on the stage of pregnancy and development of fetus. Some drugs are taken in early stage of pregnancy i.e. (15-21 days) of fertilization may not affect the fetus at all. During the early-stage fetus is highly resistant to defects. The risk of getting the fetus affected is in 3rd and 8th week after fertilization (organogenesis). The organs of fetus start developing in this major stage. During this period some drugs may cause miscarriage. The growth and maturation of fetus occurs in 9th week of fertilization. During this period drugs may alter the growth and functions of normally formed organs [3].

PHARMACOKINETICS OF DRUGS IN PREGNANCY:-

The factors which affect the low circulation of some drugs in pregnant women are women plasma volume and cardiac output and glomerular filtration rate (this increases by 30-50%). The volume of distribution of fat-soluble drugs increases due to increase in body fat during pregnancy. As plasma albumin level decreases during pregnancy increase the volume of distribution e.g. anticonvulsant thus unbound drugs are excreted more rapidly results in increase in volume of distribution [3].

PHYSIOLOGY OF PREGNANCY:-

Pregnancy is the sequence of events that begins with fertilization; proceed to implantation, embryonic development and fetal development. Pregnancy period last for 38 weeks or 40 weeks after menstrual period. Duration of pregnancy occur between 3 trimester. Trimester is the period of 3 month during pregnancy of women.

FIRST TRIMESTER:

First trimester is the most critical period in which primary germ layer develop, blood vessel formation begins, heart form and begins to develop, bone formation begins, urine secreted by fetus and mix with umbilical cord. Limb becomes distinct and digit appear. Fetus begin to move, but its movement cannot be felt by mother. Body system continue to develop.

SECOND TRIMESTER:

In this phase, fetus appears even more human like. Rapid development of body system occurs. Growth shows but lower limb continues to lengthen. Weight gain occurs and skin become pink and wrinkled. Fetus 24 week and older usually survive if born prematurely.

THIRD TRIMESTER:

In this trimester, head and body are more proportionate. Fetus assume upside down position. Body fat is 16% of total body mass. Even after birth, an infant is not completely developed and additional years is required, especially for complete development of nervous system [4, 5].

II. TERATOGENIC EFFECTS OF VARIOUS DRUGS USED IN PREGNANCY ARE AS FOLLOWS:-

Effect of thalidomide:-

Thalidomide drug was used in 1950-1960 for the treatment of morning sickness during early pregnancy. Thalidomide was first marketed in the late 1950 as a sedative and in pregnant women used for the treatment of the nausea [6]. Thalidomide causes damage to the forming embryo in a short time sensitive window also known as 'critical period'. The time sensitive window extends between 20 and 36 days after fertilization [7]. Single 50mg tablet of thalidomide during the time sensitive window is sufficient to cause birth defects in up to 50% of pregnancies. The birth defects such as limb, ear, cardiac and gastrointestinal malformation (as shown in Fig.1) occur during weeks 3 to 8 of gestation due to use of drug thalidomide [8]. The action of thalidomide ranges from day 20 to 36 post fertilization. Around 4 to 10 weeks, thalidomide was taken for relieve the symptom of morning sickness. This is time of limb development. By taking thalidomide limb deformities seen. This is known 'phocomelia' (shortened or absent long bones of limbs) [9]. Despite its tragic history, thalidomide has become the subject of major interest because of its multiple clinical value in myeloma and complication leprosy, cancer, adjuvant analgesic properties [10].

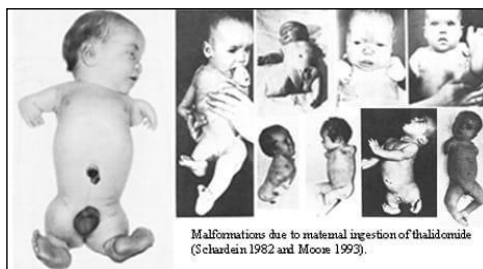


Figure 1: Birth Defect Occur Through Thalidomide.

EFFECT OF ANTIEPILEPTIC DRUG IN PREGNANCY:-

Many pregnant women with an active epilepsy need a treatment with antiepileptic drug which are also used for treating other indication such as migraine, pain syndrome and psychiatric disorders which are prevalent among women of child bearing age. These drug can cause several adverse effect on fetus such as fetal loss, intrauterine growth disorder, impaired post-natal development, congenital malformation and behavioral abnormalities (as shown in Fig 2 and Fig 3) [11]. Few of the classical teratogenic antiepileptic drug are valproic acid and phenytoin [12].

Figure 2: Birth Defect Due To Valproic Acid.

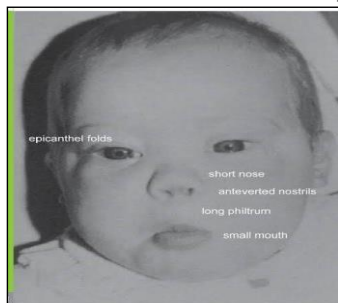
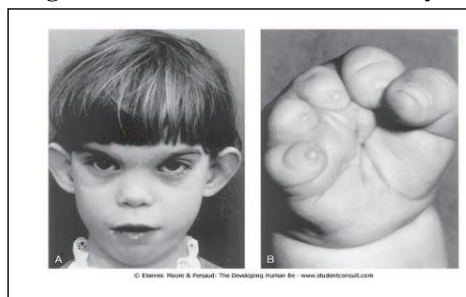


Figure 3: Birth Defect Due To Phenytoin.



Valproic acid:- Reports shows that when mice were administered high doses of valproic acid in between 200-800 mg/day, valproic acid induces various developmental defects such as skeletal defect in craniofacial bones in a dose dependent manner. Increase doses of valproic acid were also found to lead intrauterine growth retardation, craniofacial, skeletal, cardiac defects [13]. It was noted that its over doses can cause central nervous depression and many progress to coma and respiratory depression. It also shows cerebral edema [14]. Child born to a mother treated with valproic acid shows developmental delay including reduce congenital function, attention deficit disorder and learning difficulties [15].

Phenytoin:- fetal hydantoin syndrome (FHS) in fetus and new born could be caused by phenytoin, which is a hydantoin component, when expose in uterus. This disorder causes and lead to multiple dysmorphic findings such as epicanthal folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide lips, distal digital hypoplasia, intrauterine growth, retardation and mental retardation [13].

IMMUNOMODULATORY DRUGS IN PREGNANCY:-

Autoimmune disease which are more frequent in women than men are rheumatoid arthritis and systemic leupus erythematosus may occur during child bearing period.

Diseases with T helper type 1 phenotypes and disease with T helper type 2 phenotypes may flare in pregnancy in pregnancy serval changes may occur such as physiological, immunomodulatory, hormonal etc .

E.g. :- Hormonal concentration may drop rapidly and may lead to pre-inflammatory state and leads to increase the risk of rheumatoid arthritis [16].



Figure 4: Birth Defect Due To the Immunomodulatory Drug.

CORTICOSTEROIDS:

Corticosteroids therapy in pregnancy is appropriate to control clinically active maternal illness. It is the most frequently used drugs in pregnancy [17]. Epidemiological studies have said that in 1st trimester steroid should use with cleft palate but recent data does not confirm this [18].

A single course of corticosteroids is recommended for pregnant women between 24/7 weeks of gestation who are at risk of preterm delivery [19]. Corticosteroids leads to premature delivery or inhibits the growth of fetus. It also leads to increase high blood pressure, gestational diabetes, osteopenia and infections [20].

MYCOPHENOLATE:

Mycophenolate is a D category drug. Mycophenolate is an immunosuppressed drug used for many non-pregnant women to treat people with inflammatory bowel disease, inflammatory eye diseases, rheumatoid arthritis and especially used in transplantation of organ. It is a teratogenic drug for pregnant women is it is taken after 6 week of conception abnormalities can be seen like cleft lip and palate, congenital heart defects, diaphragmatic hernia, shortened figures and ears and eyes abnormalities (shown in Fig 4 and Fig 5) [21].

METHOTREXATE:

Methotrexate is use to clam to the immune system. This helps to reduce the inflammation that swollen and stiff joints in rheumatoid arthritis. If Methotrexate is used in an early pregnancy can cause miscarriage or serious birth defects or may affect the growth of the baby in womb.

The risk of poor pregnancy is due to high doses of methotrexate. Methotrexate is not prescribed because lower dose of methotrexate has also been linked to miscarriage and it is not clear whether it may cause birth defect or not. Women should get pregnant after 6 months of getting treatment of Methotrexate [22].



Figure 5: Effect of Immunomodulatory Drug on Pregnancy.

EFFECT OF SOCIAL DRUGS: -

Alcohol: - Alcohol is one of the teratogens if used by pregnant women which is transferred to baby via umbilical cord. It may result in miscarriage, disabilities in intellectual, physical and behavioral properties of pregnant women. Above mentioned disabilities are called as fetal alcoholic spectrum disorders (FASDs).

Offspring developed with FASD may show abnormal facial features (philtrum), small head size, low body weight, poor memory, intellectual disability, etc (as shown in Fig 6). Many growth and central nervous system problems can occur throughout the pregnancy, mostly baby's brain is affected by alcoholic exposure in pregnancy irrespective of times of consumption [23].

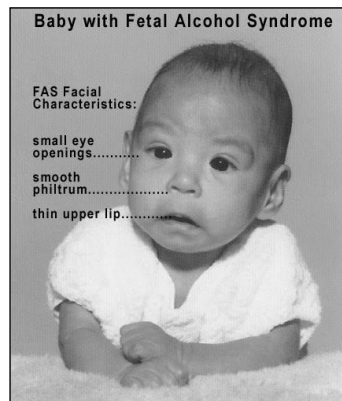


Figure 6: Birth Defect Due To Alcohol Consumption during Pregnancy.

Nicotine (smoking):- Exposure to nicotine and other compound in a cigarette smoke may increase the rate of sudden infant death syndrome (SIDS) more than usual.

In the zone of medulla oblongata serotonergic abnormalities have been discovered in SIDS Infant. As the first trimester of pregnancy is most critical and crucial period, intake of nicotine during this period may cause risk placental abruption, placenta previa, and preterm birth. Exposure to prenatal nicotine during second trimester affects dopaminergic neurological system in which it alters neurological route of neurotransmitter and acetylcholine, made fetal brain more susceptible to nicotine (figure 7), developing ADHD symptoms in fetus and adolescence [24].



Figure 7: Birth Defect Due To Nicotine.

Consequences of prenatal nicotine exposure is as follows:-

- **RESPIRATORY PROBLEMS:**
It increases asthmatic problems like tightening of the muscle around the small airways and lungs become narrow due to inflammation. The asthma symptom like cough, shortness of breath, chest tightness may be seen [25].
- **FERTILITY PROBLEMS:**
Poor oocyte function which is tied to reduce oocyte mitochondrial efficiency and increase oxidative stress which leads to infertility. In diminished ovarian reserve (DOR), the ovary loses its normal reproductive potential compromising fertility [25].
- **CANCER:**
It increases the risk of presence of malignant tumor. It can cause childhood brain tumor and leukemia, lymphoma [25].
- **NEUROBEHAVIORAL DIFFICULTIES:**
It causes exaggerated anxiety, high risk of drug addiction and ADHD [25].
- **FETAL GROWTH RESTRICTION:**
Children born have low birth weight and may have intrauterine development limitation [25].

- **CARDIOVASCULAR PROBLEM:**

It Increases the blood pressure [25].

CONCLUSION:-

Drug treatment plays very important role in curing several diseases and disorders. with the advancement of pharmaceutical science Many new drugs are being discovered which are safe and with less side effect however there are certain drugs mentioned above that can cause severe disorders in babies due to its teratogenicity, as the pregnant women consumes it. It can affect child's health and well-being and impair him/her for lifetime. Although many new safer drugs are being introduced, this area of pregnancy need more care. Thus, this article highlights the problem of teratogenicity in pregnancy and encourages researchers to develop new safer drug which will made the future generation disorder free.

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