Impact of Maternal Drug Exposure on Embroynic and Fetal Growth

Tanushri R. Borokar[1], Vijay M. Waghulkar[2], Dr Monika P Jadhav[3], S G Jawarkar[4]
[1]*Student, Dept. of Pharmaceutical Quality Assurance, Vidyabharti College of Pharmacy, Amravati*
[2,3,4]*Professor, Dept. of Pharmaceutical Quality Assurance, Vidyabharti College Pharmacy, Amravati*

***Abstract*—Maternal drug exposure during pregnancy remains a major global concern due to its potential effects on embryonic development and fetal growth. Medications taken intentionally for maternal health, as well as inadvertent exposures, may interfere with organogenesis, placental function, and fetal growth trajectories. Understanding the extent, mechanisms, and clinical relevance of these risks is essential for safer pharmacotherapy in pregnancy.**

Teratogenicity refers to structural or functional abnormalities in a developing fetus resulting from maternal exposure to certain drugs, chemicals, or environmental agents. Drug-induced teratogenic effects remain a significant public health concern, as many women require pharmacotherapy during pregnancy for acute or chronic conditions. This review provides a comprehensive evaluation of teratogenic mechanisms, including interference with cell proliferation, disruption of signaling pathways, oxidative stress, folate antagonism, endocrine imbalance, and placental transfer patterns.

***Index Terms*—Maternal drug exposure, teratogenicity, embryonic development, fetal growth, pregnancy safety, congenital anomalies**

I. INTRODUCTION

TERAS- "Monster" Genesis- "Producing". A teratogen is defined as any agent that results in structural or functional abnormalities (malformation) in the fetus, or in the child after birth, as a consequence of maternal exposure during pregnancy. Birth defects are known to occur in 3-5% of all newborns. These may include growth retardation, delayed mental development or other congenital disorders without any structural malformations. Understanding how a teratogen causes its effect is not only important in preventing congenital abnormalities but also has the potential for developing new therapeutic drugs safe for use with pregnant women. [1]

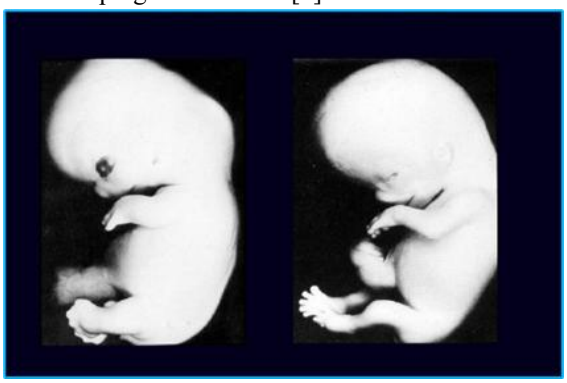

Fig:1 teratogenic effect on fetal development

Teratogen: A teratogen is something's that can cause birth defects or abnormalities in a developing embryo or fetus upon exposure. Teratogens include some medications, recreational drugs, tobacco products, chemicals, radiation, alcohol, certain infections, and in some cases, health problems such as uncontrolled diabetes in pregnant people. Exposure to a teratogen can occur through ingestion or environmental exposure during pregnancy. [1] Teratogens can begin affecting the developing embryo as early as 10 to 14 days after conception. During embryonic development, there are periods when the developing organ systems show more sensitivity to teratogens. Specifically, if exposure to a teratogen occurs during the first 3.5 to 4.5 weeks of gestation, a neural tube defect, such as spina bifida or anencephaly, may result. Various agents have been determined to not cause birth defects and are known as non-teratogenic agents. Examples of non-teratogenic agents that are commonly mistaken for teratogens include spermicides, acetaminophen, and prenatal vitamins. [2] A human teratogen is an agent that alters the growth or structure of the developing embryo or fetus,

thereby causing birth defects. Before the 1960s, many countries did not have rules about testing medications for their effects on fetuses. This changed partly because of thalidomide. This medication was given to pregnant women for nausea in the 1950s and 1960s. Between 1956 and 1962, more than 10,000 children in 46 different countries were born with birth defects, like arms and legs that had not grown. Thalidomide had not been tested well enough before it started being prescribed. Now, many countries require more testing before a medication can be said to be safe during pregnancy [3]

The first human teratogen identified in 1941 by an ophthalmologist, Norman Gregg, was maternal rubella infection in pregnancy, which produced a triad of defects (cataracts, heart malformations, and deafness) in the infants.[4]

Following the identification of thalidomide, an antinauseant, as a major human teratogen causing severe birth defects in 1961, research in teratology began to expand and there was increased awareness of the possible teratogenic impact of maternal exposures during pregnancy. Several factors that determine the teratogenicity of an exposure have been set forth as the principles of teratology by Wilson,3 guiding researchers in the study and understanding of teratogenic agents. These include, but are not limited to, the following: Abnormal development produced by a teratogenic exposure is manifested as death, malformation(s), growth retardation, or a functional disorder. These include neurologic impairments, such as mental retardation, and long-term effects on cognition and behavior that may appear later in childhood. [5]

A second principle of teratology states that susceptibility to teratogenesis varies with the developmental stage at the time of exposure, and a third claims that manifestations of abnormal development depend on dose and duration of a teratogenic exposure. These indicate that not all exposures deemed as teratogenic are actually teratogenic all the time; the timing and dose of a particular exposure during pregnancy often determine the kind and extent of its teratogenic potential. The embryonic period, during which organogenesis takes place, occurs between implantation at around 14 days to around 60 days post conception.[6]

This is usually the most sensitive period to teratogenesis when exposure to a teratogenic agent has the greatest likelihood of producing a malformation. For example, administration of many established major teratogen drugs, such as isotretinoin, valproic acid, warfarin, or high-dose methotrexate, in specific gestational windows in the first trimester is associated with a high risk of having a baby with a congenital malformation, but the risk significantly decreases in the second or third trimesters of pregnancy. In some cases, several periods of susceptibility may exist for a single organ, such as in the case of craniosynostosis, an abnormality that occurs as a result of premature fusing of cranial sutures. Also, for some teratogens, a level of exposure exists below which probably no demonstrated harmful embryonic effect occurs. [6]

Teratogenesis

A. Teratogenic agent and their effect on embryonic development.

Teratogenesis is a prenatal toxicity characterized by structural or functional defects in the developing embryo or fetus. It also includes intrauterine growth retardation, death of the embryo or fetus, and transplacental carcinogenesis in which chemical exposure of the mother initiates cancer development in the embryo or fetus, resulting in cancer in the progeny after birth. Intrauterine human development has three stages: implantation, post implantation, and fetal development. The first two stages are the embryonic stages and last through the first eight weeks after conception. The fetal stage begins in the ninth week and continues to birth So, “A teratogen is defined as any environmental factor that can produce a permanent abnormality in structure or function, restriction of growth, or death of the embryo or fetus and the study of how environmental agents disrupt normal development is called teratology”. [7]

Teratogenic exposures during prenatal development cause disruptions regardless of the developmental stage or site of action. Most structural defects caused by teratogenic exposures occur during the embryonic period, which is when critical developmental events are taking place and the foundations of organ systems are being established. [7]

Teratogenicity

Teratology is the science that investigates the congenital malformations and their causes. Intrauterine exposure to a toxicant, particularly in early pregnancy, induces embryonic and fetal changes

ranging from none up to malformations and still births.[7]

The teratogenic agents include some viral, spirochetal and protozoal infections, physical agents as ionizing radiations and excessive heat, pharmacological drugs as thalidomide, excessive vitamin A, corticosteroids, antiepileptic, antimalarial, antileishmaniasis and antihypertensive agents, industrial pollutants as toluene and cadmium, alcohol and smoking abuse, and narcotics. Maternal health problems as diabetes mellitus, multiple sclerosis and rheumatoid arthritis may also add to the etiology list of teratogenesis. The prevalence of the congenital birth defects ranges from 2 to 5% throughout the first year of postnatal life. [8]

Teratogenic Agent

A. Infectious agents:

Some infections during pregnancy are teratogenic like viral infections (e.g. rubella, herpes simplex and cytomegalovirus), spirochetal infections (e.g. syphilis), and protozoal infestations (e.g. toxoplasmosis). First trimester maternal influenza exposure is reported to be associated with raised risk of a number of non-chromosomal congenital anomalies including neural tube defects, hydrocephalus, congenital heart anomalies, cleft lip, digestive system abnormalities, and limb defects. [9]

B. Physical agents:

Radiation is teratogenic and its effect is cumulative. The International Commission of Radiology recommends pregnancy screening- tests (safe and of low cost) to all female patients of child bearing age who will undergo a radiological procedure. The degree of ionizing radiation needed for these procedures is very close to the threshold for teratogenicity, especially in the first trimester when the signs of pregnancy are not yet manifest. There is a basic assumption that risk prediction for human radiation exposure is proportional to the total radiation dose. However, there is some concern about the of dose limits for people who may be genetically cancer prone. [10]

C. Chemical agents:

Medical prescription and over-the-counter drug use are common and necessary for many pregnant women nowadays. The principal challenge of prescribing physicians is “Will these drugs induce teratogenic effects?” Such a drug-phobia arose after the eruption of thalidomide teratogenicity disaster in 1960s; when the drug was used to relieve morning, sickness associated with pregnancy. Most of medication exposures during pregnancy do not carry an increased risk of congenital malformations. [11]

Misperceptions of these risks may lead to abrupt discontinuation of therapy and even to termination of an otherwise wanted pregnancy.7 Maternal depression has a significant effect on the perception of teratogenic risk.It limits the validity of a decision-making process toward pregnancy.8–12 There is evidence for the association between health literacy and perception of teratogenic medication risk, beliefs about medications, and adherence or nonadherence to prescribed medicines during pregnancy. It was found that health literacy was significantly associated with maternal health behaviors regarding medication non-adherence. Clinicians should devote some time to inquire into their patients’ ability to understand health information, Different organ systems have different periods of susceptibility to exogenous perception and beliefs, in order to promote drug adherence during pregnancy. [11]

Factors affecting embryonic development:

I. Ethanol, Smoking, and Various Drugs:

A. Fetal Alcohol Syndrome (FAS): Patients with FAS must have three characteristics: prenatal and postnatal growth retardation (>2 SD for length and weight), facial anomalies, and CNS dysfunction. The full picture of FAS usually occurs in babies born to alcoholic mothers, or those who drink regularly or binge-drink. However, no amount of alcohol is safe. Even light or moderate drinking can affect the developing fetus. Acetaldehyde is implicated as the cause of FAS through its inhibiting effects on DNA synthesis, placental amino acid transport, and development of the fetal brain. The biologic basis for FAS is related to genetic polymorphisms identified for alcohol dehydrogenase (ADH), which converts alcohol to acetaldehyde, and acetaldehyde dehydrogenase (ALDH2), which converts acetaldehyde to acetate. [12]

B. Thalidomide: Thalidomide was used clinically in the 1960s. It caused limb reduction defects, facial hemangiomas, esophageal and duodenal atresia,

cardiac defects (ex: teratology of Fallot), renal agenesis, urinary tract anomalies. [13]

C. Chloroquine: Malformations in three half-siblings included up-slanting palpebral fissures, flat philtrum, thin upper lip, and brachy-dactyl of the fifth finger. Maternal chloroquine use during pregnancy may be associated with auditory, vestibular, retinal, and other neurologic dysfunction in children. [14]

D. Tobacco smoking: Nicotine is a vasoconstrictor that results in uterine vascular constriction and intrauterine growth retardation. The increased mortality is attributed to abruptio placentae, placenta previa, spontaneous abortion, prematurity, and IUGR. Carbon monoxide from cigarette smoking. [15]

E. Marijuana: The active ingredient of marijuana is 8,9-tetrahydrocannabinol, which is fat soluble, crosses the placenta easily, and may persist in the fetus for as long as 30 days. Growth retardation and malformations are reported after marijuana use during pregnancy, especially in the first trimester. Increased risk of non-lymphoblastic leukemia has been reported. [15]

F. Lysergic acid diethylamide (LSD): Defects of the limbs, eyes, CNS, and arthrogryposis may be present. [15]

G. Sedatives: Increased frequencies of cleft lip, cleft palate, and congenital heart disease have been reported after maternal phenobarbital exposure. Benzodiazepine-containing drugs, taken in large amounts, may produce IUGR, cleft lip, and facial features that resemble the findings of FAS, although studies have shown little or no increase in congenital anomalies. [16]

H. Isotretinoin: The risk of fetal abnormality when isotretinoin is taken by a pregnant woman is 25%. The critical period of exposure is 4 to 10 weeks of gestation. The defects include hydrocephalus, microcephaly, cerebellar dysgenesis, depressed nasal bridge, microtia or absent external ears, cleft palate, anomalies of the aortic arch, cardiac defects (including ventricular septal defect, atrial septal defect, tetralogy of Fallot), and hypo plastic adrenal cortex. [17]

II. INFECTIOUS AGENTS

Teratogen	Fertilization [days]	Malformation
Rubella virus	0-60	Cataract or heart
Thalidomide	21-40	Reduction defect of extremities
Hyperthermia	18-30	Anencephaly
Male hormones (androgen)	<90	Clitoral hypertrophy of extremities Clitoral hypertrophy
Warfarin(coumadin)	<100	Hypoplasia of nose and stippling of epiphyses
Diethylstilbestrol	>14	50% vaginal adenosis
Radioiodine therapy	>65-70	Fetal thyroidectomy
Goitrogens and iodides	>120	Fetal goiter
Tetracycline	>150	Dental enamel staining of primary teeth

Table 1: Developmental Effects of Infectious Agents

A. Influenza virus: There is no compelling evidence to incriminate influenza virus infection during pregnancy as a cause of malformations. [18]

B. Varicella: When a woman has a varicella infection during the first 20 wk. of pregnancy, there is a 2% chance that the baby will have a group of defects called the congenital varicella syndrome, which includes scars, defects of muscle and bone, malformed and paralyzed limbs, small head size, blindness, seizures, and mental retardation. [18]

C. Mumps virus: Mumps virus during pregnancy does not cause malformations, but endocardial fibroelastosis has been noted in infants with appositive mumps antigen skin test. [18]

D. Parvovirus: Human parvovirus B-19 is able to cross the placenta and results in fetal infection, which may occur whether the mother is symptomatic or asymptomatic. It is associated with a higher-than-average fetal loss and may lead to spontaneous abortion in the first trimester, hydrops fetalis in the

second trimester, and stillbirth at term. Generalized myocarditis, myositis of skeletal muscles, and abnormalities of the eyes are reported. [18]

III. RADIATION

Ionizing radiation can injure the developing embryo due to cell death or chromosome injury. The most critical exposure period is 8-15 week after fertilization. Because of its extended periods of organogenesis and histogenesis, the central nervous system (CNS) retains the greatest sensitivity of all organ systems to the detrimental effects of radiation through the later fetal stages. In utero radiation produces microcephaly and mental retardation. [19]

IV. TOXIC METALS

A. Lead: Lead crosses the placenta as early as the 12th to 14th weeks of gestation and accumulates in fetal tissue. The adverse effects of lead include spontaneous abortion and stillbirth. A small but significant increase in minor malformations, including hemangiomas, lymphangiomas, hydroceles, skin tags, skin papillae, and undecided testes, was seen in infants with high lead levels in the umbilical blood. [20]

B. Mercury: Methyl mercury poisoning produces atrophy of the granular layer of the cerebellum and spongiosa softening in the visual cortex and other cortical areas of the brain, polyneuritis can also occur. [20]

C. Lithium: The ratio of lithium concentrations in umbilical cord blood to maternal blood is uniform. Infants with high lithium concentrations (>0.64 mmol/L) at delivery have significantly lower Apgar scores. [20]

V. CHEMICAL EXPOSURES

A. Polychlorinated and polybrominated biphenyls (PCBs): Poisoning have infants with parchment-like skin with desquamation and brown discoloration (“cola baby”), dark colored nails, conjunctivitis, low birth weight, exophthalmos, and natal teeth. [21]

B. Toluene: Toluene embryopathy includes prenatal and postnatal growth deficiency, microcephaly, anencephaly, developmental delay, cardiac and limb defects, and craniofacial anomalies similar to fetal alcohol syndrome (FAS). [21]

VI. MATERNAL CONDITIONS

A. Obesity: During pregnancy, obesity is associated with adverse outcomes that include macrosomia, hypertension, pre-eclampsia, gestational diabetes mellitus (GDM), and fetal death. [22]

B. Diabetes mellitus: Hyperglycemia leads to inhibition of the myoinositol uptake that is essential for embryonic development during gastrulation and neurulation stages of embryogenesis. Deficiency of myoinositol appears to cause perturbations in the phosphoinositide system that lead to abnormalities in the arachidonic acid-prostaglandin pathway. [23]

C. Cretinism and iodine deficiency: There is a role of maternal T4 in neurological embryogenesis, before the onset of fetal thyroid function and, therefore, its protective role in fetal thyroid failure.

In early pregnancy, iodine deficiency induces a critical decrease of T4 levels with consequent TSH increase responsible for hypothyroidism in about 50% of iodine-deficient pregnant women. Congenital hypothyroidism associated with deafness and mental retardation is found in the offspring of hypothyroid mothers. Deafness persists in spite of thyroid replacement therapy. [24]

D. Phenylketonuria: Maternal phenylketonuria (PKU) leads to defects that include intrauterine and postnatal growth retardation, cardiovascular defects, dislocated hips, and other anomalities. [24]

Teratogenesis in fetal malformation

Teratogenic Genesis in Fetal Malformations

Congenital anomalies can occur during the developmental stages of the embryo, from abnormal genetics passed on from the parents or from vivid environmental factors. Teratogenic factors pose a greater risk to the fetus, as these abnormalities may go undetected until birth. These malformations are the origin of the infant's postnatal illness and disability. The defects can also lead to mortality. The loss can also affect families, as they are affected by not only the loss but also financially. Most of the teratogenic-induced anomalies, once detected, maybe rehabilitated naturally. Those who do require medical intervention pose their own risks, similar to those of infections. Therefore, environmental exposure to teratogens can

create long-lasting effects that range from infertility, intrauterine growth restriction, structural defects, and functional central nervous system abnormalities that may lead to fetal death.[25]

Genetic Susceptibility to Drug Teratogenicity:

A. Genetic Susceptibility Associated with Drug Teratogenicity:

Congenital anomalies are the leading cause of infant mortality in high-income countries and the second most common cause in many middle-income countries. such conditions emerge during fetal development and can be inherited or influenced by environmental factors, such as medication exposure. The prescription of drugs during pregnancy is common; with a prevalence of 40% to 80% in Western countries Drugs used by the mother during pregnancy can be teratogenic, causing abnormal development of the embryo or fetus.[26]

Drugs	Major congenital malformation
Doxycyclie	Increased risk for cardiac malformations and ventricular/atrial septal defect
Erythromcin	Nephrotic system malformations
Macrolides	Digestive system disorders
Moxifloxacine	Respiratory abnormalities
Ofloxacin	Major congenital malformations
Phenoxymethylpenicillin	Nervous system malformations
Quinoline	Urinary system abnormality
Tetracycline	Permanent discoloration of a child's teeth and bone disorders
Warfarin	Eye and Hand defect and growth retardation

B. Antidepressants:

Antidepressants, in particular serotonin reuptake inhibitors (SRIs) examined in eight out of nine studies, was the most investigated class of drug in the literature on genetic variations associated with adverse drug effects in utero. SLC6A4, which encodes the serotonin transporter, was a commonly investigated gene in studies on genetic vulnerability for a wide range of different antidepressants and phenotypic outcomes. [27]

C. Thalidomide:

Thalidomide was the main individually investigated drug. All studies have been performed by the same research group in the approximately same sample of individuals. Were reported to be associated with an increased risk of developing thalidomide embryopathy, a phenotypic spectrum of malformations characterized by limb reduction defects. [28]

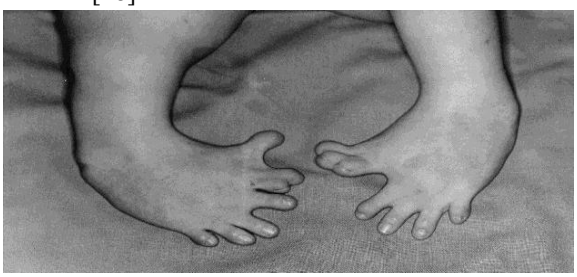

Fig 2: fetal deformity due to thalidomide

D. Antiepileptic Drugs:

MTHFR, associated with folate metabolism, was the most frequently investigated gene in studies on the genetic susceptibility to AED teratogenesis. The most commonly studied AEDs were valproic acid, carbamazepine, and phenytoin. Upon AED exposure, the maternal genetic variant rs1801133 of MTHFR was associated with an increased risk of major malformations and fetal anticonvulsant syndrome in the children [29]

9.Teratogenic Medications:

During the last decades, it has become deeply understood that drugs administered to the mothers during pregnancy might have detrimental effects on the physical development of the fetus. Thalidomide is a well-described example of how a seemingly innocent, over-the-counter medication for the morning sickness could exert such a deleterious effect on the fetus, such as miscarriages, and physical deformities. Since 2015, for the better categorization of drug safety, FDA uses the Pregnancy and Lactation Labeling Rule (PLLR), replacing the "A, B, C, D, X " pregnancy labeling categories. The gestational age of the embryo at the time of exposure is the determining factor for the nature of the defect, making the first trimester, the period of organogenesis, the most precarious period for significant malformations. The

scope of this article is to present the most important teratogenic medications and their mechanism of action comprehensively. [29]

A. Neurological Medications:

Medications for neurologic conditions are among the drugs with the highest teratogenic potential. One of the most commonly prescribed drug categories in pregnant women is antiepileptic drugs (AEDs), used primarily to prevent seizures, but also for neuropathic pain, migraines, and psychiatric disorders. AEDs in low doses can cause cognitive defects and, in higher doses, cause structural malformations. Phenobarbital, an inducer of CYP450 2B and 3A genes, at a molecular level, produces free radicals and causes DNA bases transversion while macroscopically, results in impaired growth, motor development, and fetal mortality. Valproate poses a higher teratogenic threat compared to the other AEDs and potentially can distort the development of the fetus. It can lead to cardiac anomalies, neural tube defects, dominantly spina bifida, and developmental delay. It may also cause the fetal valproate syndrome, a rare clinical condition consisting of characteristic facial dimorphisms linked to valproate exposure, limb abnormalities, lip/cleft palate, and urinary tract defects. The teratogenicity of valproic acidic exerted via the inhibitory actions of folate and histone deacetylase, through increased accumulation in embryonic circulation, as well as by the production of reactive oxygen species (ROS). Carbamazepine is useful for the treatment of epilepsy and bipolar disorder during pregnancy. [30]

B. Antimicrobial Medications:

Antimicrobials are among the most generously prescribed medications during pregnancy and lactation. Hence, clinicians should demonstrate great attention to the dose and type of drug administered to pregnant women, due to pharmacokinetic alterations during this period and the potential harm they could pose to the fetus. Primarily, chloramphenicol is a bacteriostatic drug that binds to the 50s subunit of prokaryotic ribosome's and thus, interferes with protein synthesis. [30]

According to the available data regarding the toxicity of chloramphenicol to fetuses and newborns, there is a potential danger of bone marrow suppression in direct proportion to dose. Also, it may lead to the development of gray baby syndrome, a syndrome characterized by abdominal dilatation, vomiting, hypothermia, cyanosis, and gray color of the baby's skin. This syndrome has a high prevalence among premature infants because of their reduced ability for renal and liver metabolism (primarily glucuronidation) of chloramphenicol. [30]

C. Anticoagulants:

Coumarin derivatives, e.g., warfarin antagonizes vitamin K, and inhibit γ-carboxylation of glutamyl residues, reducing protein binding ability with calcium. This inhibition during fetal development could explain the skeletal abnormalities, the stippled calcification of epiphysis, and the nasal hypoplasia. Depending on the severity of nasal hypoplasia, choanal atresia osteoporosis could also be present, leading to respiratory and feeding problems. Central nervous system malformations may also occur with the administration of coumarin anticoagulation since they cross the placenta, inhibit clotting factors, and mainly cause intracranial hemorrhage. The risk of congenital disabilities associated with fetal warfarin syndrome (FWS) is particularly high during the 6-9 gestational weeks. [31]

D. Vitamin A

Vitamin A, in large doses, can also be teratogenic. A pregnant woman can receive an excessive amount of vitamin A by eating excess food or by taking nutrient supplements with Vitamin A or drugs containing retinoid. Not only the overdose but also the lack of them can cause embryonic malformations. Retinoic acid is essential for early embryogenesis and subsequently for maturation and development of tissues and organs. [31]

E. Hormonal Medication

Diethylstilbestrol (DES) is a nonsteroidal estrogen drug that acts by inhibiting the hypothalamic-pituitary-gonadal axis. DES was being prescribed in pregnant women for three decades, to prevent pregnancy miscarriage. Research later showed that it could potentially be a carcinogen oreven a teratogen upon prenatal exposure. The women exposed in utero to DES developed clear cell adenocarcinoma of vagina and cervix and structural anomalies in the genital tract. Besides, the sons of women who received DES during

pregnancy developed several abnormalities of the genital tract.[31]

VII. CONCLUSION

The pharmaceutical management of pregnant women requires special consideration and close collaboration from physicians, to prevent any harmful effects for both the mother and the fetus. Having the disastrous squeal of thalidomide in mind, clinicians should be quite cautious while prescribing any drug to pregnant women and be aware of the new data about drug safety during pregnancy.

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