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A Comprehensive Review on Drugs Induced Teratogenicity During Pregnancy

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ABSTRACT

A congenital malformation is an anatomical or structural abnormality present at birth. Congenital malformations may be caused by genetic factors or environmental insults or a combination of the two that occur during prenatal development. Most common congenital malformations demonstrate multifactorial inheritance with a threshold effect and are determined by a combination of genetic and environmental factors. During the first 2 weeks of gestation, teratogenic agents usually kill the embryo rather than cause congenital malformations. Major malformations are more common in early embryos than in newborns; however, most severely affected embryos are spontaneously aborted during the first 6 to 8 weeks of gestation. During organogenesis between days 15 to 60, teratogenic agents are more likely to cause major congenital malformations.

1. INTRODUCTION

Teratogens are substances that may produce physical or functional defects in the human embryo or fetus after the pregnant woman is exposed to the substance [1]. Teratogenesis signifies the structural malformations during fetal development, in distinction from other kinds of drug-induced fetal damage such as growth retardation, dysplasia (e.g. Iodine deficiency-related goiter), or the asymmetrical limb reduction. Alcohol and cocaine are examples of such substances [2]. Approximately 3-5% of live births are complicated by a birth defect each year totaling around 1.2 lakh babies. Drug use is an uncommon cause of birth defects, but certain medications can increase the likelihood of developing a birth defect (Table 1) [3-6]. Additionally, more women taking any kind of medication have more than doubled in the last 30 years. Current evidence suggests that between 65 to 94% of women take at least one prescription drug during pregnancy. Nearly 70% of women are taking medication in the first trimester during organogenesis [7]. On average, women are taking three medications in pregnancy with over 50% of women using four or more. Thalidomide was marketed in 1957 for morning sickness and nausea and soon became the ‘drug of choice to help pregnant women’. It went into general use by the following year and was widely prescribed in Europe, Australia, Asia, Africa and the Americas [8]. Allegedly, the drug was harmless and a lethal dose could not even be established. However, in the early 1960s, in what might be described as the worst case of pharmaceutical oversight, the drug was found to be associated with a congenital abnormality causing severe birth defects in children born of women who had been prescribed this drug during pregnancy [9]. More than 10 thousand cases of birth defects were reported in over 46 nations following thalidomide exposure. Children were born with missing (Amelia) or abnormal (Phocomelia) legs, arms, feet, and hands (Figure 1); spinal cord defects; cleft lip or palate; absent or abnormal external ears; heart, kidney, and genital abnormalities; and abnormal formation of the digestive system [10,11]. It is estimated that 40% of thalidomide victims died within a year of birth. The exposure of teratogenic chemicals prior to conception, during prenatal or postnatal development leads to manifestations of developmental toxicity, including the death of the developing organism, structural abnormality, altered growth, and functional deficiency. This includes over the counter medications and herbal supplements. People had sought explanations for abnormal human and animal development, however, for centuries, and they had developed different theories about the causes for the abnormalities [12]. There are a variety of causes of congenital malformations including Genetic factors (chromosomal

abnormalities as well as single gene defects), Environmental factors (drugs, toxins, infectious etiologies, and mechanical forces), and Multifactorial etiologies including a combination of environmental and genetic factors. The graph below (Figure 2) divides these etiologies by percentages [13].

Table No. 1: List of the drugs whose use is contraindicated during pregnancy along with the harmful/damaging effects they may produce on the fetus.

Sr. No.	Chemical substances (generic name)	Teratogenic effects
1	Captopril	Intrauterine growth retardation, Fetal death, Neonatal anuria, Hypoplastic calvaria.
2	Diclofenac	Premature closure of the ductus arteriosus, Decrease in the fetal number, Skeletal and heart defects.
3	Estrogen	Masculinisation of the female fetus, Behaviour changes like rough-and-tumble play.
4	Phenytoin	Fetal antiepileptic drug syndrome, Distal phalanges hypoplasia, Spina bifida, Abnormal nasal bridge, and ears, Abnormal motor development.
5	Methotrexate	Skeletal defects, Low birth weight, Disturbed neurulation.
6	Isotretinoin	Craniofacial abnormalities, Hydrocephalus, Encephalocele, Mental retardation.
7	D-penicillamine	Cutis laxa, Fetal malformations, and death.
8	Thalidomide	Phocomelia and Amelia, Anotia/microtia, Hearing loss.
9	Warfarin	Nasal hypoplasia, Spontaneous abortion, Distal limb hypoplasia, Central nervous system defects, and neurological abnormalities.
10	Caffeine	Expression of several abnormal phenotypes.
11	Neural tube closure	Craniofacial malformations, Malformations of the limbs and digits
12	Organophosphate	Neural tube defect, Shortening of pregnancy, Decrease in baby birth weight (length and head), Anencephaly or spina bifida.
13	Glyphosate	Shortening of the anterior-posterior axis, Microcephaly, Microphthalmia, Cyclopia, Craniofacial malformations.
14	Cytomegalovirus	Mental retardation, Oculo-auditory lesions, Hepatosplenomegaly (thrombocytopenia).
15	Rubella	Congenital rubella syndrome, Cataracts, Sensorineural deafness, Congenital heart disease Intrauterine growth retardation, Retinopathy.
16	Cyclopamine	Cyclopia, Holoprosencephaly
17	Lambda carrageenan	Exencephaly, Abnormal beak, Anophthalmia, Rachischisis
18	Ionizing radiation	Microcephaly, Skeletal defects, Mental retardation, Hydrocephaly, Microphthalmia, Optic atrophy and cataracts, Mutations of germ cells.

19	Cigarette smoking	Intrauterine growth retardation, Perinatal mortality, and morbidity, Cardiac defects, Chromosomal anomalies, Central nervous system defects.
20	Lead acetate	Mental retardation, Nephrotoxicity, Miscarriages and stillbirths, Menstrual disturbances, Spontaneous abortion.
21	Methylmercury	Minamata disease, Cerebral palsy, and mental retardation, Sensorimotor dysfunction.
22	Sulfur mustard	Disruption of nucleic acids and proteins, Selective cell death of ocular (respiratory and cutaneous tissues), Antimitotic (mutagenic, carcinogenic and cytotoxic effects).
23	Alcohol	Fetal alcohol syndrome.
24	Cocaine	Abruption of the placenta, Disruptive defects on cardiovascular and autonomic systems.

Figure No. 1: Thalidomide drug causes Amelia or Phocomelia in the fetus.

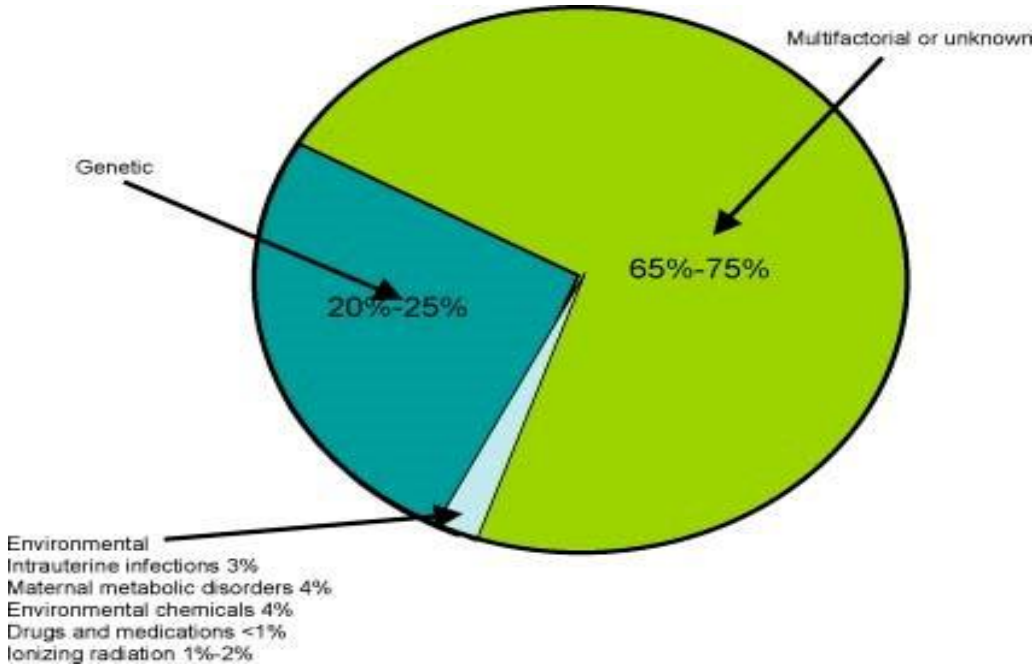

Figure No. 2: Different types of congenital malformations etiologies by the percentages.

2. EFFECT OF DRUGS ON PREGNANCY

Gestation may be divided into four major stages (Table 2) [14,15]. The United States Food and Drug Administration (USFDA) established in 1979, Five letter risk categories- A, B, C, D or X to indicate the potential of a drug to cause birth defects if used during pregnancy (Table 3&4) [16-20]. The categories were determined by assessing the reliability of documentation and the risk to benefit ratio [21]. These categories did not take into account any risks from pharmaceutical agents or their metabolites in breast milk. On the drug product label, this information was found in the section 'Use in Specific Populations' [22,23].

Table No. 2: List of the major stages of gestation.

Sr. No.	Stages	Description
1	Pre-implantation stage (blastocyst formation)	Lasts 16 days; i.e. from conception to implantation. Shows "all-or-none" effect; i.e. either killing the embryo or not affecting it at all. No teratogenesis.
2	Period of organogenesis (from 17th to 56th day)	During this period, drugs may produce no measurable effect; abortion; a sub-lethal gross anatomic defect; or a permanent subtle metabolic or functional defect.
3	Second and Third trimesters	Drugs can cause teratogenicity or other effects such as retardation of physical or brain growth, behavior defect, premature labor, neonatal toxicity or even post-natal effects such as cancer in later life.
4	Labor-delivery stage	The danger of toxicity in the neonatal period.

Table No. 3: List of drugs regarding pregnancy and lactation labeling by the USFDA category.

Sr. No.	Pregnancy category	Description
1	Category A	No risk in controlled human studies: Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters). Example drugs or substances: levothyroxine, folic acid, liothyronine.
2	Category B	No risk in other studies: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester. Example drugs: metformin, hydrochlorothiazide, cyclobenzaprine, amoxicillin, pantoprazole.
3	Category C	Risk not ruled out: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks. Example drugs: tramadol, gabapentin, amlodipine, trazodone.
4	Category D	Positive evidence of risk: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks. Example drugs: lisinopril, alprazolam, losartan, clonazepam, lorazepam.
5	Category X	Contraindicated in pregnancy: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh potential benefits. Example drugs: atorvastatin, simvastatin, warfarin, methotrexate, finasteride.
6	Category N	FDA has not yet classified the drug into a specified pregnancy category.

Table No. 4: List of the commonly used drugs during pregnancy along with their categories as per FDA categorization.

Sr. No.	Drugs (generic name)	Category
1	Analgesics and Antipyretics	B and C
	Acetaminophen	B
	Phenacetin	B
	Aspirin	C
2	Antiemetics	B and C
	Dimenhydrinate	B
	Meclizine	B
	Doxylamine	B
	Cyclizine	B
3	Antibiotics	B, C, and D
	Penicillin, Ampicillin, Amoxycillin	B
	Erythromycin	B
	Amikacin	C/D
	Cloxacillin, Cephalosporins	B
	Tetracyclines	D
	Sulfonamides	B/D
	Streptomycin	D
	Gentamicin	C
4	Amoebicides	B
5	Antimalarials	C
6	Anthelmintics	B
7	Antifungals	C
8	Antituberculosis	B and C
	Pyrazinamide	C
	Ethambutol	B
	Rifampicin	C
	Isoniazid	C
	P-aminosalicylic acid	C
9	Vitamins B, C, D, E, folic acid	A
10	Hormones	A, X and D
	Androgens	X
	Estrogens	X
	Norethindrone	X
	Norgestrel	X
	Thyroxin	A
	Progestogens-Hydroxyprogestrone	D
	Medroxyprogestrone	D
11	Bronchodilators	C

3. CONCLUSION

Drug use during pregnancy is an almost inevitable event. Some of the drugs may have adverse effects on the baby of exposure. The unique nature of the physiology of pregnancy presents a challenge for the pharmaceutical treatment of chronic and acute disorders and for symptom management of many complaints associated with pregnancy. It is the responsibility of all clinicians, including pharmacists to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. Counseling women who have had exposure to drugs about the risk of teratogens involves accurately identifying exposure and quantifying the magnitude of exposure.

Conflict of interest

The authors have declared that no conflicts of interest exist.

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