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Teratogenic Effect of Various Drugs At Different Stages of Pregnancy

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Abstract:
The Greek word "Terato," which means monster, is the root term of "teratogenesis." An individual who undergoes teratogenesis develops morphological abnormalities. These could include illness without structural abnormalities, such as intelligent disability. Exposure to the specific chemicals during the pregnancy may cause birth defects or fetal deformities, including behavioral or emotional issues, IQ deficiencies, physical abnormalities, etc. Significant abnormalities are more common in the early embryo than in newborns because teratogenic are most likely to cause harm between 15-16 days during organogenesis. Numerous drugs are available, and most of the commonly used ones during the pregnancy may have teratogenic consequences in different stages of pregnancy. The first three trimesters of the pregnancy are frequency distinguished. The first trimester of the pregnancy is when the medication is more effective. All who are at risk of becoming pregnant should have common ailments treated with attention, as it is the most crucial time before the gestation period is formed. Prescription drug usage is common during pregnancy, but the teratogenic risk to humans is unclear for more than 90% of medications that have been licensed in the United States in the last few years. Many mechanisms and potential exposures, including drugs, may contribute to a specific birth abnormality. Understanding the teratogenic mechanisms linked to various medications is the main emphasis of this review.

Keywords: Teratology, patents, Embryo deformity, Etiology.

Introduction:

A process known as Teratogenesis results in birth abnormalities or deformities in an embryo or fetus. Teratology is the study of the underlying mechanisms and causes of birth abnormalities or malformations. These could include conditions like an intellectual disability that doesn't have any visible structural abnormalities. A teratogen is an external substance that results in birth abnormalities or deformities [1].

In general, teratogenicity or reproductive toxicity relates to the development of detrimental biological effects on the reproductive system that could be affected by exposure to chemicals or several environmental agents, such as changes to the reproductive organs of either males or females, which are associated with pregnancy outcomes or the endocrine system [10].

Chemicals known as "Teratogens," which have the potential to cause birth defects, are frequently utilized as active ingredients in medication. These chemicals cause pregnancy-related flaws or abnormalities in the fetus [11]. Teratogens include pharmaceuticals like thalidomide, environmental pollutants like cadmium, and environmental contaminants such as endocrine-disrupting substances and pesticides. Other causes of teratogenesis include poor diet, physical constriction during pregnancy, and viruses such as the Zika and rubella viruses. The processes by which teratogens cause birth abnormalities or malformations

are investigated using animal models, which can also provide information about normal development. Making safer and more tailored therapeutic medications also requires understanding teratogenesis [1]. Some factors that promote Teratogenicity are depicted in Figure 1.

The several teratogen types are:

- Chemicals, including prescription drugs like retinoic acid and thalidomide; illegal drugs like cocaine and alcohol; pollutants like pesticides connected to fertility and reproduction diethylstilbesterol during pregnancy; and environmental contaminants such heavy metals like cadmium.
- Infections, including as rubella and Zika virus.

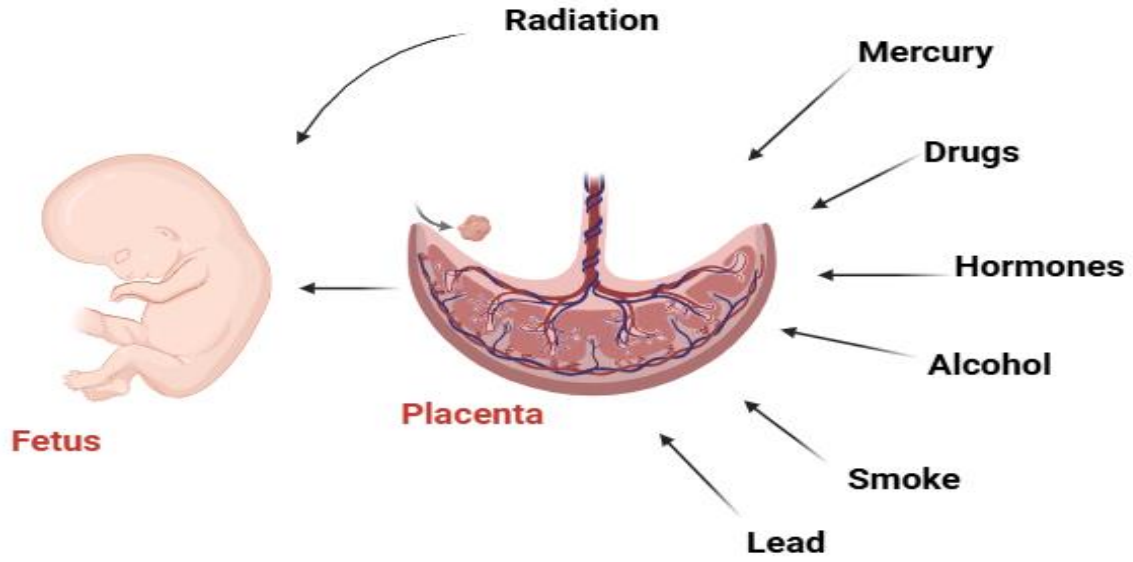


Figure1: Factors promoting teratogenicity.

- In oligohydramnios, where the amniotic fluid is lost and the fetus is constrained, physical constraint or in-utero injury, such as clubfoot, may develop. A fetus may sustain physical injury while still inside the mother, such as amniotic band syndrome. When the condition is severe, it can be fatal.
- Hyperthermia
- Maternal conditions like gestational diabetes [2-9].

History of Teratology:

In 1928, experimental teratology was first reported in a study that found that pregnant women who get therapeutic radiation exposure develop microcephaly in their unborn children. Teratology as a modern science began in the 1930s with the publication of a number of experiments using pregnant pigs fed a diet deficient in vitamin A[12-23].

In 1990, two teratology information centres were founded.

1. Organization of Teratology Information Specialists (OTIS)
2. European Network of Teratology Information Services (ENTIS)

Teratogens were identified after elevated incidences of birth defects and abnormalities. For instance, thalidomide, a medication with a teratogenic effect, was used to treat morning sickness in

the 1960s. A thorough understanding of the teratogenic background and risk is necessary to prevent or slow the rate of teratogenic effects. [24,25].

Year	Event
1905	The first experimentally induced developmental toxicity in mammals. Embryonic lethality induced by X-rays in cats.
1921	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by a lipid diet.
1928	The first experimentally induced teratogenicity in mammals. Disorders in limbs in pigs induced by a lipid diet.
1929	The first description of malformations in humans caused by exogenous factors. Microcephalia caused by X-ray irradiation of the pelvis.
1933	Deficiency of vitamins occurs in the first month before pregnancy and during pregnancy.
1995	Recognition of food deficiency leading to malformations in animals. Eye disorders in pigs due to hypovitaminosis.

Table 1: Various important events in the history of teratogenesis [31].

How Do Researchers Examine Teratogenic Events?

The goal of experimental teratology is to simulate human conditions/malformations in animal embryos and, when applicable, in vitro cell culture experiments to comprehend the condition. Possible therapeutic approaches can also be tested using this methodology.

Several fundamental concepts that were initially outlined by Wilson in 1959 (see Cassina et al., 2012; Schardein, 2000) must be understood to comprehend how an agent generates teratogenic event. These consist of the following:

- The embryo's genetic background determines its susceptibility to an agiventeratogenic substance and subsequent atogenesis because embryos, like adults, display variations in the how individuals react to medications, agents, etc.
- When they are exposed to the agent, usually The damage is more severe the earlier in embryonic development the exposure takes place, especially between weeks 2 and 8, when the majority of the major tissues and organs are growing and being patterned.

Stages of Fetus development:

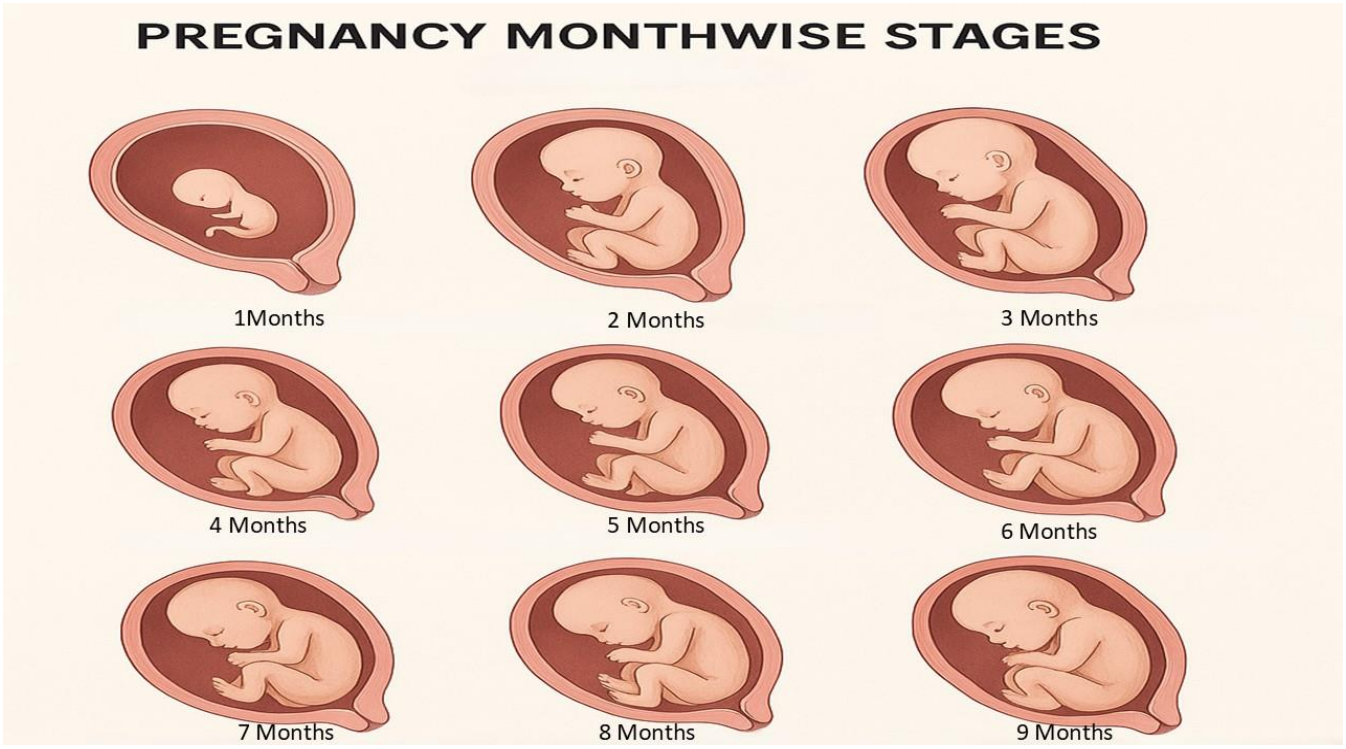


Figure 2: Stages of pregnancy

First Trimester (0–14 weeks):

Following fertilization, the egg splits into a ball of cells and embeds itself in the uterine lining **(3–4 weeks after the last menstrual cycle)** This marks the beginning of life as an embryo, and by this point, the embryo measures 0.2 mm. [26,27,28.29].

The embryo has assumed a C shape by weeks five and six, and the development of the brain, spinal cord, and a basic beating heart has started (**5-6 weeks**).

By 7 to 8 weeks,

The brain has grown fast, giving the skull a disproportionate size, the heart has grown into four chambers, fingers and toes have formed, and basic muscle development has begun. Early structures for arms, legs, eyes, and ears have also started to emerge.

The embryo changes into a fetus with all major body parts developed by **11–12 weeks**.

By 14 weeks,

The fetus weighs around 1.5 ounces and is about 3.5 inches long.

Second Trimester (15-26):

The limbs grow, the fetal body begins to straighten, and outward characteristics like eyelashes and nails take shape.

Around 17 to 18 weeks, movements are noticeable; this is known as “quickening”.

Development of face characteristics, lungs, and fingerprints; by 24 weeks, the fetus is around 8.5 inches long.

Third Trimester (27-40): Fat builds up beneath the skin, the lungs mature, and the brain develops significantly. The fetus, which weighs an average of 7.5 pounds, is ready for delivery by 37 to 40 weeks,

when the lungs are almost fully grown.

Etiology of Teratogenesis:

Teratology is the area of embryology that focuses on determining the cause of aberrant embryonic development. Many teratogens contribute to the development of congenital abnormalities in two etiological groups: (1) mainly environmental, (2) multifactorial [31].

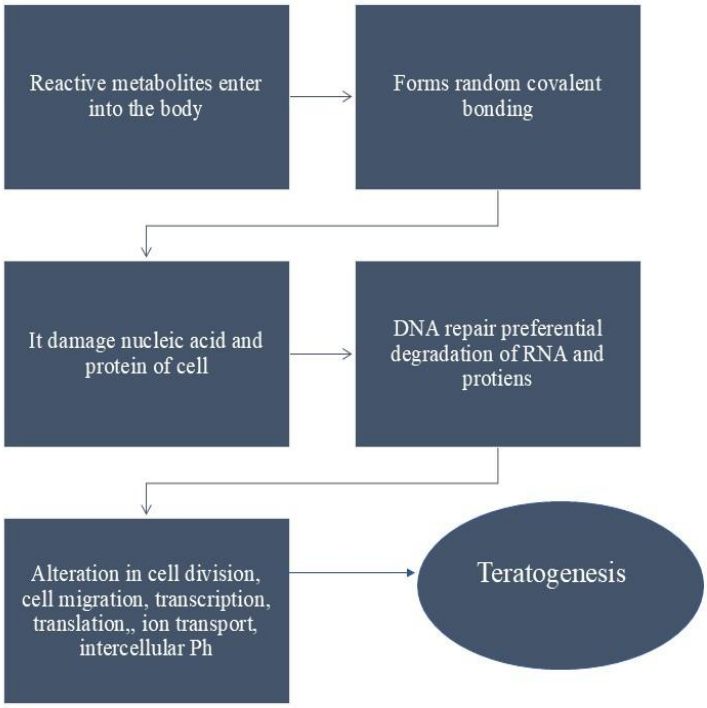


Figure 3: Etiology of the Teratogenicity.

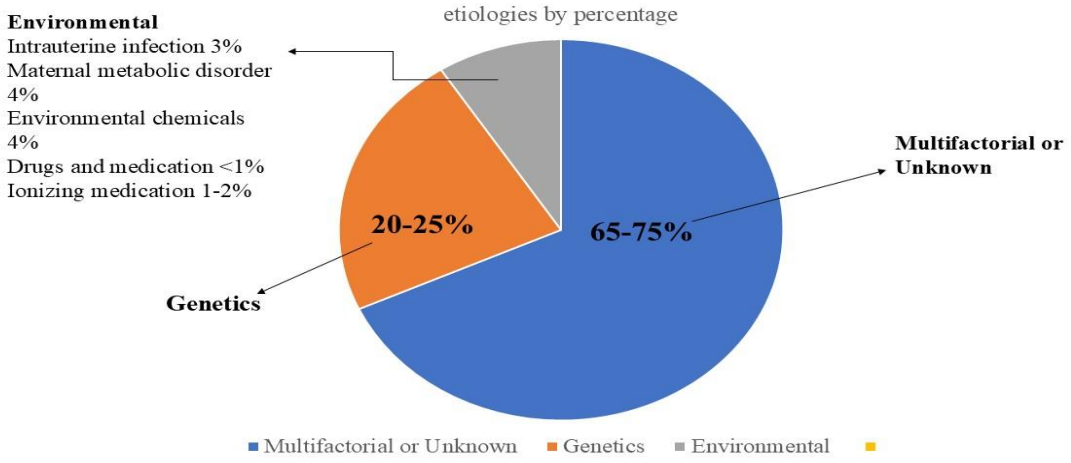


Figure 3: Etiology by percentages [32].

Pregnancy stages	Affected organs/ system	Examples of Teratogenic Drugs
Pre-implantation (0-2 weeks)	All or none (survival or death)	High dose radiation or Methotrexate
Embryonic period (3-8 weeks)	Major Congenital malformation	Thalidomide, Isotretinoin, warfarin
Fetal period (9-12 weeks)	Functional abnormalities, Growth retardation	Alcohol, Phenytoin, Valproic acid
Late pregnancy (13+ weeks)	CNS damage, Growth Retardation, Withdrawal Syndrome.	NSAIDS, ACE inhibitors, opioids

Table 2: Teratogen effect in the different stages of pregnancy.

The effects of teratogenic drugs on the Growth of the fetus: The drug's effects depend on the fetus's developmental stages, potency, and dosage.

The effectiveness of a medication also depends on the dosage that reaches the fetus. This dosage depends on a number of factors, including the mother's dosage, the drug's distribution in her bloodstream, placental function, the mother and fetus's genetic and physiological conditions, and exposure to other drugs, toxins, or environmental hazards.

- They may also alter the way the placenta functions, usually by accelerating the expansion of blood vessels and decreasing the quantity of oxygen and nutrients the fetus gets from the mother.
- They could unintentionally hurt the fetus by causing preterm labor, reducing blood flow, or forcing the uterine muscles to contract rapidly. Exposure to teratogens during fetal development is responsible for 4% to 5% of congenital disorders. Additionally, studies have shown that exposure to teratogens affects both cognitive and physical development[25].

List of contraindicated and safe medicines drugs and agents with their teratogenic effect:
A list of safe drugs during pregnancy.

Sr. No.	Safe Drugs (in pregnancy)	Function	Side effects (in fetus)
1.	Analgesic drugs (Paracetamol, pethidine, Indomethacin, Alopurinol)	Analgesic, antipyretic, chronic arthritis and connective tissue disorder, gout and kidney stones.	No fetal abnormalities, Administered at the first stage of labor 6-8hrs before delivery).
2.	Gastro-intestinal agent (laxative, antiemetic, anti-diarrheal).	Benefits in constipation, Inhibit action of emetics, diarrhea.	No teratogenic or adverse effect, Treatment of morning sickness during first trimester, Anti-spasmodic during pregnancy.

3.	Antiasthmatic agent (Ephedrine, Aminophylline, Terbutaline).	Asthma, hay fever, bronchial asthma, Chronic asthma	No adverse effect and teratogenic effect.
4.	Antihypertensive agent (Methyldopa, Hydralazine, Lidocaine).	Hypertension, Congestive heart failure, Cardiac arrhythmia.	Decrease fetal wastage, Increase birth weight and length of gestation, No adverse effect.
5.	Antitubercular agent (Isoniazid).	Tuberculosis infection treatment	Decrease fetal wastage, Increase birth weight and length of gestation, No adverse effect.
6.	Anti-coagulants(heparin).	Anticoagulant action.	Avoids fetal neural damage
7.	Folic Acid	Prevents neural tube defects	Nausea, bloating, allergic reactions (rare)
8.	Prenatal Vitamins	Supports maternal and fetal health	Nausea, constipation, dark stools (due to iron)
9.	Acetaminophen (Tylenol)	Pain relief, fever reduction	Liver toxicity (high doses)
10.	Doxylamine + Pyridoxine (Diclegis, Bonjesta)	Treats morning sickness	Drowsiness, dry mouth, dizziness
11.	Calcium Carbonate (Tums)	Relieves heartburn	Constipation, bloating
12.	Magnesium Hydroxide (Milk of Magnesia)	Treats constipation	Diarrhea, dehydration with excessive use
13.	Fiber Supplements (Metamucil, Psyllium Husk)	Relieves constipation	Bloating, gas, cramps
14.	Ondansetron (Zofran) (use with caution)	Treats nausea and vomiting	Headache, constipation, QT prolongation (rare)
15.	Insulin	Controls blood sugar in diabetes	Low blood sugar (hypoglycemia)
16.	Labetalol	Treats high blood pressure	Fatigue, dizziness, low blood pressure

17.	Methyldopa	Lowers blood pressure	Drowsiness, dry mouth, depression (rare)
18.	Metformin (for gestational diabetes)	Lowers blood sugar	Stomach upset, diarrhea
19.	Cephalexin (Keflex)	Treats bacterial infections	Nausea, diarrhea, yeast infections
20.	Azithromycin	Treats bacterial infections	Stomach upset, diarrhea
21.	Amoxicillin	Treats bacterial infections	Nausea, diarrhea, allergic reactions
22.	Penicillin	Treats bacterial infections	Allergic reactions, diarrhea
23.	Erythromycin	Treats bacterial infections	Nausea, stomach cramps
24.	Clindamycin	Treats bacterial infections	Diarrhea, risk of C.difficile infection

25.	Heparin (Unfractionated or LMWH - Enoxaparin/Lovenox)	Prevents blood clots	Bleeding risk, bruising
26.	Thyroxine (Levothyroxine, Synthroid)	Treats hypothyroidism	Palpitations, sweating, weight loss (if overdosed)
27.	Famotidine (Pepcid)	Treats acid reflux & heartburn	Headache, constipation
28.	**Ranitidine** (formerly recommended but recalled)	Treats acid reflux	Withdrawn due to safety concerns

29.	Diphenhydramine (Benadryl)	Allergy relief, sleep aid	Drowsiness, dry mouth
30.	Loratadine (Claritin)	Treats allergies	Drowsiness (less than Benadryl)
31.	Cetirizine (Zyrtec)	Treats allergies	Mild drowsiness
32.	Chlorpheniramine	Treats allergies	Drowsiness, dry mouth

33.	Budesonide (inhaled, Pulmicort)	Treats asthma	Throat irritation, Hoarseness

34.	Albuterol (Ventolin, ProAir, Proventil)	Treats asthma	Increased heart rate, jitteriness
35.	Guaifenesin (Mucinex) (avoid in 1st trimester)	Treats cough	Nausea, dizziness
36.	Dextromethorphan (Robitussin DM)	Cough suppressant	Drowsiness, dizziness
37.	Oxybutynin (Ditropan) (use with caution)	Treats urinary incontinence	Dry mouth, insomnia, weight changes
38.	Hydroxyzine (Vistaril, Atarax) (use with caution)	Treats anxiety, nausea, itching	Drowsiness, dizziness
39.	Bupropion (Wellbutrin) (considered when needed)	Treats depression & smoking cessation	Dry mouth, insomnia, weight changes
40.	Sertraline (Zoloft) (preferred SSRI in pregnancy)	Treats depression & anxiety	Nausea, headache, sexual dysfunction
41.	Citalopram (Celexa) (use with caution)	Treats depression & anxiety	Risk of QT prolongation at high
42.	Fluoxetine (Prozac) (use with caution)	Treats depression & anxiety	Insomnia, nervousness, potential withdrawal effects in newborn

List of contraindicated drugs:

Sr no.	Drug name	Trimester effect	Teratogenic Effects
1.	Isotretinoin	All trimesters	Severe birth defects, CNS malformations, cardiovascular abnormalities
2.	Thalidomide	First trimester	Limb deformities (phocomelia), ear malformations
3.	Methotrexate	First trimester	Neural tube defects, limb defects, craniofacial abnormalities
4.	Warfarin	First and second trimester	Nasal hypoplasia, CNS abnormalities, bleeding risks
5.	ACE inhibitors (e.g., Enalapril, Lisinopril)	Second and third trimester	Renal dysplasia, oligohydramnios, skull hypoplasia
6.	ARBs (e.g., Losartan, Valsartan)	Second and third trimester	Fetal renal failure, oligohydramnios, lung hypoplasia
7.	Tetracyclines	Second and third trimester	Teeth discoloration, bone growth retardation
8.	Fluoroquinolones	All trimesters	Cartilage damage, joint deformities
9.	Valproic acid	First trimester	Neural tube defects (spina bifida), facial abnormalities
10.	Carbamazepine	First trimester	Neural tube defects, craniofacial abnormalities

11.	Phenytoin	First trimester	Fetal hydantoin syndrome (Growth deficiency, cleft palate, limb defects)
12.	Misoprostol	First trimester	Moebius syndrome (cranial nerve defects, limb defects)
13.	NSAIDs (e.g., Ibuprofen, Aspirin)	Third trimester	Premature closure of ductus arteriosus, oligohydramnios
14.	Chloramphenicol	Third trimester	Gray baby syndrome (circulatory collapse)
15.	Aminoglycosides (e.g.,Gentamicin, Streptomycin)	All trimesters	Ototoxicity, nephrotoxicity
16.	Androgens (e.g., Testosterone, Danazol)	First trimester	Masculinization of female fetus, genital abnormalities
17.	Diethylstilbestrol (DES)	First trimester	Vaginal adenocarcinoma, uterine abnormalities in offspring
18.	Sulfonamides	Third trimester	Kernicterus (bilirubin displacement), haemolysis in G6PD deficiency
19.	Trimethoprim	First trimester	Neural tube defects (folate antagonist)
20.	Lithium	First trimester	Ebstein's anomaly (heart defect)
21.	Methimazole	First trimester	Aplasia cutis congenita (scalp defects)
22.	Propylthiouracil (PTU)	First trimester	Possible fetal goitre, hypothyroidism
23.	Ergotamines (e.g., Ergotamine, Dihydroergotamine)	All trimester	Uterine contractions, miscarriage risk
24.	Statins (e.g., Atorvastatin, Simvastatin)	All trimesters	CNS and limb abnormalities, impaired cholesterol synthesis
25.	Benzodiazepines (e.g., Diazepam, Lorazepam)	First trimester	Cleft palate, neonatal withdrawal syndrome
26.	Cocaine	All trimesters	Placental abruption, growth restriction, preterm labor
27.	Alcohol	All trimesters	Fetal alcohol syndrome (growth restriction, facial abnormalities, CNS defects)
28.	Opioids (e.g., Morphine, Codeine, Oxycodone)	All trimesters	Neonatal withdrawal syndrome, respiratory depression
29.	Tobacco (Nicotine)	All trimesters	Low birth weight, preterm birth, SIDS risk

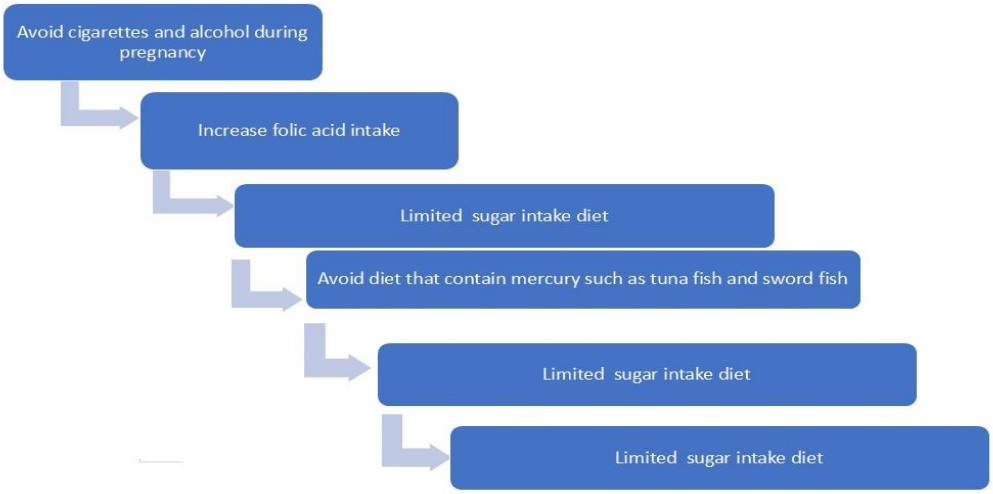
FDA Rating System:

In 1979, the United States Food and Drug Administration (FDA) introduced a system of rating pregnancy risk associated with pharmacological agents, which categorized all drugs approved after 1983 into one of five pregnancy risk categories (A, B, C, D, and X). Category A includes drugs having no risk to the foetus in the first trimester whereas Category B shows no risk in animal studies and lacks human studies. Category C &D produce adverse effect on animal and humans respectively, but can be used when potential benefit outweighs the risk. In 2015 the FDA replaced the former pregnancy risk letter into These Pregnancy and Lactation Labelling Final Rule (PLLR) which is being implemented.

Following the thalidomide tragedy in 1979, which involved over 10,000 children, the FDA released the categories A, B, C, D, and X based on the amount and calibre of research conducted on the medication (not on its safety during pregnancy or use). The FDA later made changes, and as of right now, all prior classifications are eliminated from all drug labels for drugs that will remain on the market for the next three to four years, including those that were introduced after June 2015. Their subsections state that "pregnancy" encompasses those who are in labor till delivery. Pregnancy exposure registry, risk summary, clinical considerations, and statistics are all included in this section. It also provides important information about birth control or pregnancy testing before to, during, or following medication therapy. These data relate to medications that have known clinical effects on the baby and should not be taken while nursing.

Pregnancy category	Level of evidence	
A	No risk in 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 risk in later trimesters).	None
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.	Nevertheless, because the studies in humans cannot rule out the possibility of harm, [name of drug] should be used during pregnancy only if clearly needed
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 use of the drug in pregnant women despite potential risks.	[Name of drug) should be given to a pregnant woman only if clearly needed
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 use of the drug in pregnant women despite potential risks.	If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus
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 use of the drug in pregnant women clearly outweigh potential benefits.	[Name of drug] is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus

How to stop Teratogenesis:



These days, teratology is a significant issue that requires fresh ideas and approaches to prevent. There is no treatment for teratogenesis once the kid is born, although it can be avoided by avoiding teratogens during the various phases of pregnancy. The best thing is pregnancy counselling strategy to stop teratogens. Making lifestyle changes, including quitting smoking, and managing long-term medical issues are made possible by pregnancy planning plus a lot more.

Conclusion:

Knowing how teratogenesis occurs is crucial for preventing such occurrences, identifying those at risk early, and developing treatment plans. Experimenting Teratology provides information on normal development by illuminating pathways that may be compromised by substances like medications, genes, or environmental factors. It is nevertheless evident that the developing embryo is delicate, especially during the early stages of embryogenesis when the body plan is being formed and the tissues and organs are maturing. Agents, medications, and compounds used in the workplace and environment must be examined to make sure they are not carcinogenic or that pregnant women shouldn't be exposed to them. Ideally, via research on teratogenic substances. Because of the unique physiology of pregnancy, managing symptoms and giving medicine for both acute and chronic diseases can be difficult indicating a variety of pregnancy-related problems. Providing patients with thorough, accurate, and up-to-date information regarding the risks and benefits of taking medicine during pregnancy is the duty of all medical providers, including pharmacists. For precise and successful identification of exposure and determination of exposure levels, women who have used drugs must be counseled of their risk of teratogens. When it comes to illegal narcotics, this may be more challenging than when prescribing medications. Furthermore, despite the possibility of more modern alternatives, long-used drugs are typically advised due to their proven fetal safety.

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