



Teratogenic Effect Of Different Drugs At Different Stage Of Pregnancy And Effect By Ayurvedic Medicine

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Abstract

The process of human development begins at fertilization, where a sperm penetrates the egg, forming a single cell known as a zygote. This marks the start of embryonic development, with crucial stages such as organogenesis occurring. Pregnancy spans 9 weeks, divided into three trimesters. Managing medications during gestation and lactation is challenging, as drugs can potentially harm the growing fetus or lactating baby. The first trimester is especially sensitive to medications, necessitating caution in treating common ailments for women at risk of pregnancy. Unfortunately, around 3-5% of live births face birth defects, totaling approximately 8,000 babies. Certain medications, like tetracycline and Thalidomide, can cause serious abnormalities such as teratogenicity, microcephaly, hydrocephalus, spina bifida, and various other conditions. Some Ayurvedic herbs might have unknown effects on pregnancy. Lack of scientific research makes it hard to determine their safety during pregnancy. Pregnant women should always consult knowledgeable healthcare providers before using any Ayurvedic remedies. Individual factors, including the woman's health, the specific Ayurvedic medicine, and the pregnancy stage, all play a role in potential effects. Some Ayurvedic herbs and preparations are avoided during pregnancy due to their potential effects on the uterine muscles or hormonal balance. This composition aims to

provide current and reliable information on drug usage during pregnancy, offering an updated perspective on the guidelines set forth by the US Food and Drug Administration (FDA) regarding gestation and lactation.

Keywords :- fertilization, fetus Teratogenic drug, drug used in pregnancy, ayurvedic medicine used in pregnancy.

Introduction:

Teratogenicity is a reproductive toxicity is defined as adverse effects of a chemical or drug substance on sexual utility and fertility in adult males and females in addition to development of toxicity in the progeny.

Development toxicity shows adverse toxic effects to the embryonic fetus. Chemicals or drugs produce development toxicity by two procedure:

- Firstly, they can act straight on cells of the embryo or fetus resulting in cells death or cell damage , most important development of the abnormal organs.
- Secondly, they can act indirectly and may induce a mutation in a germ cell death or which is transferred to the fertilized ovum. Some mutated fertilized ova develop into abnormal embryos.

The 3 basic types of development toxicity:

Embryolethality : It is recognized by various effects shown by humans like failure to conceive, unprompted abortion, or stillbirth.

Embryotoxicity : It is recognized by various effects like growth retardation or delayed growth of specific organ system.

Teratogenicity : It is recognized as irreversible situation that permanent birth defects in live off spring.

Teratogenicity is an expression of development toxicitu, representing a particular case of embryo or fetotoxicity, by the introduction or the augmentation of the frequency of structural disorders in the progeny.[1]

Dose evaluator for teratogenicity

Characteristically, a NOAEL or LOAEL can be obtained from TERATOGENIC toxicity studies. NOAEL/LOAEL can be further used for quantitative risk evaluation.

- No Observed Adverse Effect Level (NOAEL): The maximum exposure level at which there are no biologically major augmentation in the severity of adverse affect among the exposed inhabitants and its suitable control; some effects may possibly be created at this level so but they are not considered as adverse effects.

- Lowest Observed Adverse Effect Level (LOAEL): The least exposure levels at which there are biologically major augmentation in severity of adverse effects among the exposed inhabitants and table control group.
- The units of NOAEL or LOAEL: mg/kg/bw/day or ppm.

Teratogenic testing guidelines

Reproductive or development toxicity screening assay (OECD TG 421)

Prenatal development toxicity test (OECD TG 414)

Two generation reproduction toxicity study (OECD TG 416)

Extended one generation reproductive toxicity study (EOGRTS; TG 443).[1].

In recent decades, the understanding of the impact of maternal drug use during pregnancy on fetal development has deepened significantly. A prominent case in point is Thalidomide, once considered a harmless over-the-counter remedy for morning sickness, which tragically led to miscarriages and severe physical deformities in fetuses.[2] To enhance drug safety categorization, the FDA introduced the Pregnancy and Lactation Labeling Rule (PLLR) in 2015, replacing the previous "A, B, C, D, X" labeling system. The specific timing of exposure during gestation, particularly during the first trimester, the critical period of organogenesis, plays a pivotal role in determining the nature of fetal defects. This article aims to comprehensively explore key teratogenic medications and their underlying mechanisms of action.[3].

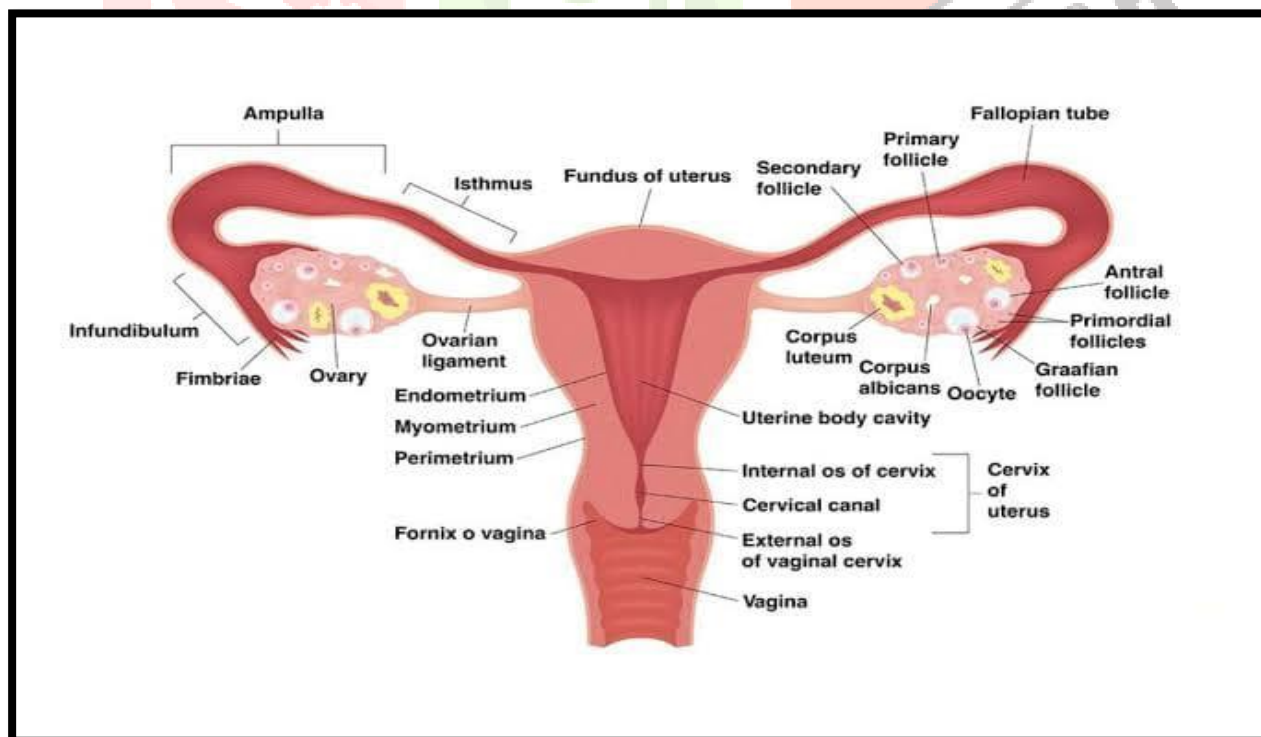


Figure no. 1 female reproductive system

There are four stages of development of pregnancy

1. Fertilization
2. Development of the blastocyst
3. Development of embryo
4. Development of fetus and placenta

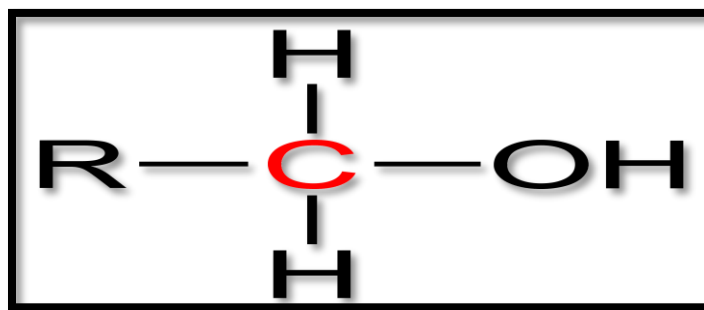
- **List of some drugs whose use is contraindicated during pregnancy which may affect they may produce on the foetus**

1. Alcohol

Introduction : Antenatal alcohol exposure (AAE) poses immediate and enduring risks, exerting toxic and teratogenic effects on an individual's development and well-being. Alcohol, acting as a toxic substance, can induce a range of physical and neurological abnormalities in the fetus, leading to persistent behavioral impairments and other complications that can extend into the individual's lifetime.[4] Recent research has focused on unraveling the mechanisms underlying alcohol's immediate teratogenic impact on fetal development and understanding the pathways through which it contributes to long-term health issues and susceptibility to diseases later in life. The teratogenicity of alcohol has been substantiated in humans through rigorous laboratory investigations, epidemiological studies, and controlled experiments on animals.[5]

Mechanism of action: The enzyme alcohol dehydrogenase (ADH) converts alcohol to acetaldehyde, which inhibits DNA synthesis, amino acid transport from placenta to the fetus, besides interfering in brain development. The susceptibility is related to the amount of ADH, which have variations in their expression due to genetic differences in ADH alleles[6]

Teratogenic effect: Deficiency in intrauterine growth and postnatal growth, cognitive abnormalities, leading to a set of characteristics called fetal alcohol syndrome (FAS), characterized by: alterations in facial appearance such as small palpebral fissures, large epicanthic folds, small head, small upper jaw, smooth philtrum, thin upper lip etc , decreased muscle tone, poor coordination, heart defects (ventricular and atrial septal defects), late reasoning, speech, movement and social skills development. FAS is the main cause of intellectual disability.[7].



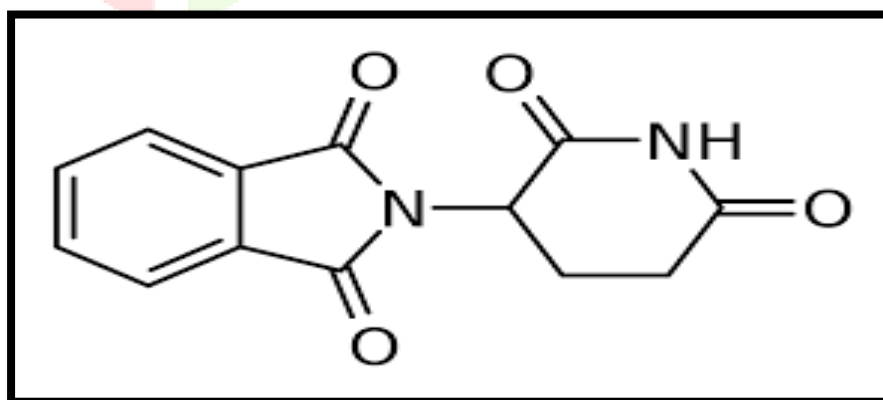
Structure No. 1. Alcohol

2. Thalidomide

Introduction : Thalidomide, once widely used in the late 1950s and early 1960s to treat nausea in pregnant women, led to severe birth defects in thousands of children. Discovering their pregnancy often prompts individuals to reconsider their medication, but thalidomide's product label advises against its use during pregnancy. Despite potential risks, consulting healthcare providers before altering medication is crucial. They can weigh the benefits of treatment against the risks of untreated illness during gestation.[8]

Mechanism of action Thalidomide, a notorious human teratogen, inhibits angiogenesis by affecting the IGF-I and FGF-2 pathways. It stimulates the transcription of integrin subunit B3 genes, promoting angiogenesis in limb buds and root growth.[9]

Teratogenic agents: Thalidomide exposure results in phocomelia, pre-axial polydactyl, trifa langeal thumb, facial hemangiomas, esophageal and duodenal anomalies, cardiac defects, renal agenesis, urinary tract anomalies, genital defects, dental anomalies, ear abnormalities, facial palsy, ophthal moplegia, exophthal mia, and microphthal.[10]



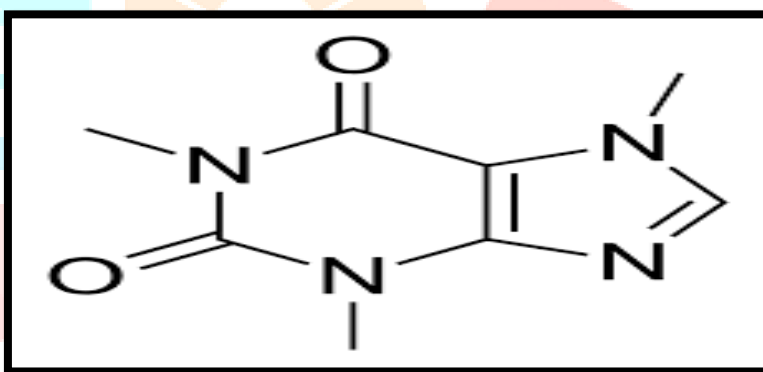
Structure No. 2. Thalidomide

3. Caffeine

Introduction Caffeine, a chemical present in various foods and beverages like coffee, tea, and cola, affects the nervous system and can lead to restlessness and sleep disturbances. However, it's considered safe for pregnant or breastfeeding women to consume up to 200 mg per day. The impact of caffeine during gestation and fetal development depends on maternal intake and caffeine metabolism speed. Previously, experts recommended limiting daily maternal caffeine intake to 300 mg, but recent EFSA guidelines suggest reevaluation.[11]

Mechanism of action Caffeine, a xanthine alkaloid, easily crosses the placenta, reaching the fetal circulation. It stimulates the central nervous system, increasing motor activity and triggering the release of catecholamines, adrenaline, and noradrenaline. Additionally, it influences serotonin turnover in specific areas and inhibits phosphodiesterase activity, contributing to its varied effects.

Teratogenic agents CNS defects, orofacial clefts, structural skeletal defects, cardiovascular malformations, adactyly and absence of thumbs.[12]



Structure No. 3. Caffeine

4. Marijuana

Introduction : Marijuana is the lawless medicine most generally used during gestation. The tone- reported frequency of marijuana use during gestation ranges from 2 to 5 in utmost studies but increases to 15 – 28 among youthful, civic, socioeconomically underprivileged women 1 2 3 4 5. Advanced rates of use are set up when querying women at the time of delivery rather than at antenatal visits because some druggies may not seek attention care.[13]

Mechanism of action It's major psychoactive element, Marijuana crosses the placenta and accumulates in fetal brain, potentially harming CNS development, marijuana use in early gestation is associated with confinement and cognitive abnormalities at age 10 in the seed, similar as lower Command and literacy disabilities, memory impairment.[13]

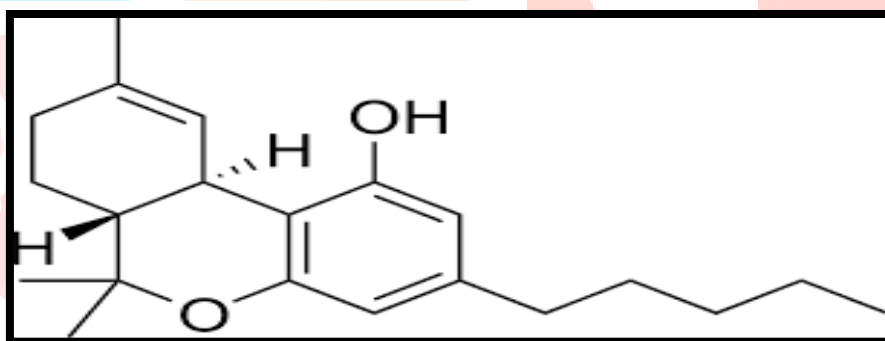
Teratogenic agents Intrauterine growth restriction, cognitive and neurobehavioral imbalance respiratory and hormonal disorders.[14].

5. LSD (Lysergic acid diethylamide)

Introduction Lysergic acid diethylamide (LSD) is a substance known for inducing altered states of consciousness and vivid hallucinations. Its effects can manifest physically, leading to elevated blood pressure, rapid heart rate, and dilated pupils. LSD is typically consumed orally, although it can also be administered through injection or inhalation methods. This potent substance has been explored for its mind-altering properties, but its use comes with various physiological responses and potential health risks.[15]

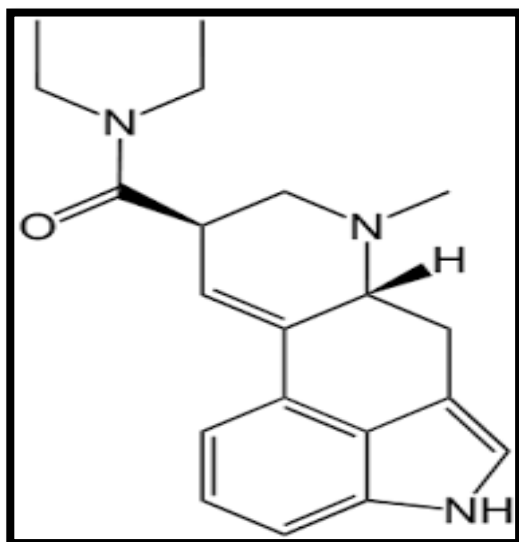
Mechanism of action LSD (lysergic acid diethylamide) disrupts the brain's functioning, causing distortions in psychic, circulatory, and thermal processes. Its complex interactions with neural pathways lead to profound alterations in perception and cognition, affecting various physiological functions.

Teratogenic agents LSD exposure poses grave risks, potentially resulting in brain damage, abnormalities in the lower jaw, alterations in facial contours, defects in limbs and eyes, joint problems, and an increased likelihood of miscarriage. These teratogenic effects underscore the critical importance of avoiding LSD during pregnancy, as it can lead to a range of severe developmental abnormalities and health complications in the unborn child.[16].



Structure No. 4. Marijuana

Structure No. 5. LSD



➤ Teratogenic drugs and agents

No.	Medicine / chemical class	Medicine/ chemical agent	Effect	recommendation
1	ACE	Catopril, enalapril, fosinopril sodium, lisinopril hydrochloride, ramipril.	Second and third-trimester exposure to ACE inhibitors is associated with oligohydramnios, hypocalvaria, anuria, renal failure.	Avoid in the second and third trimester.
2	Alcohol	Alcohol	Mental retardation, intra uterine growth retardation, small head, foetal alcohol,; syndrome characterized by maxillary hypoplasia, congenial heart disease.	Do not use during pregnancy.
3	Antibiotics	Tetracycline	Yellow straining of teeth and diminished growth of	Avoid during second and

			the long bones.	third trimester.
4	Antibiotics	Nitrofurantoin	Has haemolytic effect on the new born when used in the last trimester	Avoid in term
5	Anti- coagulant	Warfarin	Crosses the placenta and causes bleeding in the foetus resulting into spontaneous abortion, stillbirth, neonatal death, and pretern birth. Cause birth defects like mental retardation, blindness etc	Avoid during pregnancy especially in the first and third trimester.
6	Antifungal	Fluconazole	Congenital abnormalities when used in first trimester at high doses e.g. malformed bones	Avoid during pregnancy.

Table No. 1

➤ Ayurvedic medicine for diseases of pregnancy

Pregnancy signifies the fertilization and development of one or more offspring, referred to as an embryo or fetus, within a woman's uterus. Multiple gestations, such as twins or triplets, can occur during pregnancy. Childbirth typically happens around 38 weeks after conception, translating to approximately 40 weeks from the last normal menstrual period (LNMP) for women with a four-week menstrual cycle. Human pregnancy is extensively researched compared to other mammalian pregnancies.

Ayurvedic medicinal products encompass plant-derived substances like leaves, roots, and flowers, used in various forms for preventive or curative treatments. While these products have historical roots in Asia, Africa, and Latin America, their popularity has surged in North America and Europe in recent decades. Despite the lack of comprehensive efficacy and safety data, the use of ayurvedic medicinal products is widespread.

Women, especially during pregnancy, are significant users of herbal medicinal products for health maintenance and disease treatment. Reports indicate that between 10 and 74% of pregnant women in regions like Africa,

Australia, Europe, the United Kingdom, and the United States use herbal medicinal products. In the UK, around 40% of pregnant women employ these products to address pregnancy-related issues or enhance nutritional intake for better pregnancy outcomes. This trend continues into the postnatal period, where 31% of breastfeeding women rely on complementary and alternative medicines, including herbal products, to manage various ailments or improve milk flow.

- **Madeephalarasayana:**

Very useful for pregnant women for vomiting, sensation, nausea.

Dosage: 5ml to 10ml. to be used daily.



Figure No. 2.Madeephalarasayana

- **Sindurabhushanam(10gm)**

A boon to pregnant women, in nausea and vomiting, feeling of heat in the body and uneasiness and other symptoms generally appear.

Ingredients: 1. Abhrakabhasma (Sataputa), 2. Rasa Sindura, 3. Suddha Gandhaka, 4. Suddha Tankana

Dosage: 1g = 4 doses to be used twice daily by adding equal quantity of dried jeeraka powder with Madeephalarasayana/Draksharista.



Figure no. 3. Sindurabhushanam(10gm)

- **Swarnamaliniivasantarasa**

Can be used for pregnant ladies in all cases of cough and fevers.

Dosage: to be taken with equal quantity of water in 10ml dosages after meal.

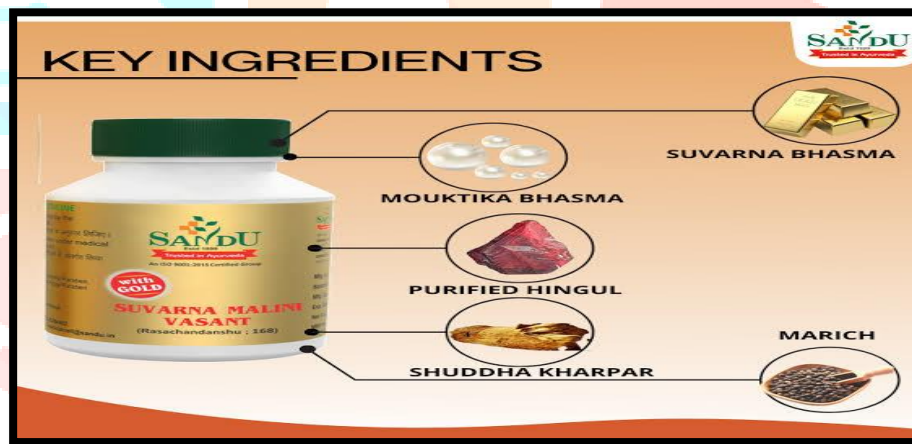


Figure No. 3. Swarnamaliniivasantarasa

For better results use this ayurvedic medication for a minimum period of 3 months.

Diet: according to the constitution of the body, diet follow-up is essential for health and longevity. Every patient should observe precautions in diet the time of usage of the medicine to avoid aggravation and to obtain speedy results.

Conclusion

In conclusion, comprehending the mechanisms behind the induction of birth defects is crucial for devising preventive strategies. Enhancing the accuracy of experimental animal extrapolation can refine the assessment of compound risks for human birth defects. Identifying human teratogens provides opportunities for proactive prevention, mitigating potential exposures.

Additionally, Ayurvedic treatments for infertility focus on ensuring successful conception and a healthy, full-term pregnancy leading to the birth of a normal, healthy baby. Through the study of Swarnamalinivasantarasa from both literary and practical perspectives, it becomes evident that understanding the causative factors of diseases is paramount. Avoiding these factors, combined with adopting a healthy diet and exercise regimen, disrupts the chain of pathogenesis. This concept, known as Nidana Parivarjana, serves as the initial step in disease treatment. By embracing this approach, natural eradication of the disease's progression occurs, making it an invaluable strategy in the realm of treatment.

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20. Figure 4. Swarnamalinivasantarasa
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21. Table 1 Teratogenic drugs and agents
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