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TERATOGENIC EFFECTS OF DIFFERENT DRUG AT DIFFERENT STAGES OF PREGNANCY

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1 ABSTRACT

In the evolving landscape of modern medicine, teratogenicity has gained renewed attention due to the rising prevalence of drug exposure during pregnancy, both intentional and unintentional. With the advancement of pharmacotherapy, women of reproductive age are increasingly prescribed complex medication regimens, leading to a higher risk of fetal developmental toxicity. Teratogenic effects arise when drugs interfere with normal embryonic or fetal development, resulting in congenital anomalies, growth retardation, or functional disorders. The outcome largely depends on the timing of exposure—where the embryonic period (3rd to 8th week) is most critical for organ formation, while the fetal stage is sensitive to functional and growth disturbances. This review explores the stage specific teratogenic mechanisms of diverse drug classes such as antiepileptics, retinoids, anticoagulants, ACE inhibitors, antibiotics, and chemotherapeutic agents. It further highlights recent trends emphasizing the role of pharmacogenomics, artificial intelligence, and predictive modeling in identifying teratogenic risks before clinical manifestation. Additionally, emerging issues like polypharmacy, selfmedication, and environmental drug contamination are discussed as novel contributors to developmental toxicity. The unique perspective of this review lies in connecting classical teratogenic knowledge with modern predictive science to support safer drug design and personalized therapy during pregnancy. Future research focusing on

molecular biomarkers and AI-driven teratogen screening could revolutionize prenatal drug safety and minimize preventable birth defects.[1,2,3]

KEYWORDS: Teratogenicity, Pregnancy, Pharmacogenomics, Artificial intelligence, Polypharmacy, Congenital anomalies, Predictive toxicology, Pharmacovigilance, Digital health.

2 INTRODUCTION

Teratogenicity refers to the ability of an agent (drug, chemical, infection, or physical factor) to produce congenital malformations or functional deficits in the developing embryo or fetus. Druginduced teratogenesis remains a major concern in clinical practice and public health because many pregnant patients require medication for chronic or acute conditions, and prenatal exposure can lead to lifelong disability, neurodevelopmental impairment, or fetal loss. A review that examines how different drugs exert teratogenic effects at specific stages of pregnancy helps clinicians balance maternal benefit against fetal risk, informs counselling, and guides safer prescribing.

Teratogenicity refers to the ability of an agent such as a drug, chemical, infection, or physical factor to produce congenital malformations or functional deficits in the developing embryo or fetus Drug-induced teratogenesis remains a major concern in clinical practice and public health, as many pregnant women require medication for chronic or acute medical conditions. Prenatal exposure to certain drugs can lead to irreversible outcomes such as growth retardation, structural malformations, neurodevelopmental impairment, or even fetal loss. Therefore, understanding drug safety during pregnancy is essential to ensure both maternal well-being and fetal protection.

The susceptibility of the embryo or fetus to teratogenic agents largely depends on the stage of pregnancy at the time of exposure. During the pre-implantation stage, drug exposure may cause “all-or-none” effects, whereas the organogenesis period (3^{rd}–8^{th} week) poses the highest risk for major congenital malformations. Exposure during the fetal stage (after the 8^{th} week) generally results in growth retardation or functional deficits rather than gross structural defects. Various drugs including antiepileptics, retinoids, anticoagulants, and antineoplastic agents are known to produce teratogenic outcomes through mechanisms such as interference with cell differentiation, DNA synthesis, or oxidative stress. Hence, this review focuses on evaluating the teratogenic potential of different drugs across the stages of pregnancy,

emphasizing mechanisms, clinical consequences, and strategies for safer pharmacotherapy in pregnant women.[4,5]

3 WHAT IS A TERATOGEN?

A teratogen is any substance, drug, chemical, infection, or physical agent that can cause structural or functional abnormalities in a developing embryo or fetus when exposure occurs during pregnancy. The severity and type of defect depend on factors such as the dose, timing of exposure, genetic susceptibility, and maternal health conditions.[6,7,8]

4 HISTORICAL BACKGROUND OF TERATOLOGY

The study of birth defects, or teratology, dates back to ancient civilizations, where congenital anomalies were often attributed to supernatural or moral causes. Modern scientific teratology began in the 20th century, particularly after the thalidomide tragedy (1950s–1960s), which led to thousands of infants born with limb deformities due to prenatal drug exposure. This event marked a turning point, prompting stricter drug safety regulations, establishment of pregnancy risk categories, and deeper investigation into developmental toxicology.[9,10]

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.

5 ETIOLOGY OF TERATOGENESIS (TRENDING AND UNIQUE)

Teratogenesis is a multifactorial phenomenon resulting from the complex interplay between genetic predisposition, environmental exposure, and maternal physiological conditions. The etiological factors of teratogenesis have evolved from being viewed as purely chemical or drug- induced to involving intricate molecular, cellular, and epigenetic mechanisms that disrupt the highly coordinated process of embryonic development.[14,16]

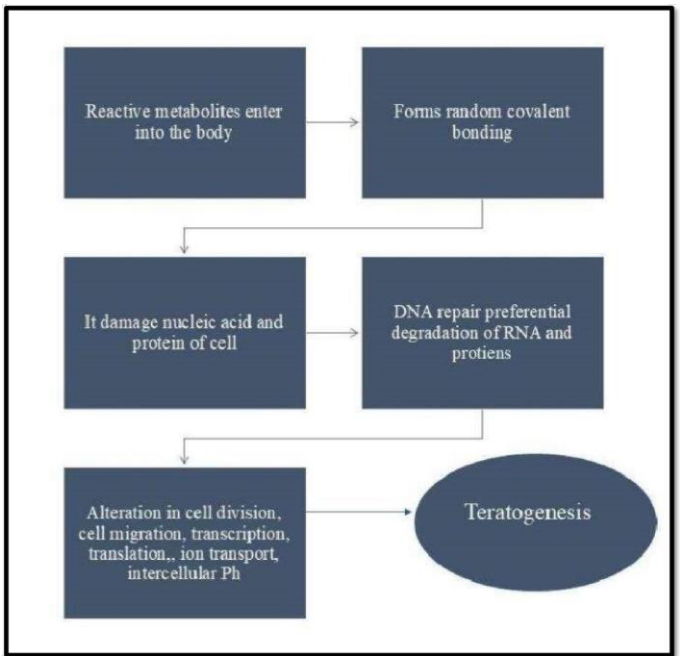

Fig. 1: Etiology of the Teratogenicity.

- **Etiology of Teratogenicity (with Percentage Contribution)**

Teratogenicity results from a wide variety of causes that interfere with normal embryonic or fetal development. Epidemiological data suggest that most congenital malformations are multifactorial, involving both genetic and environmental influences. The approximate contribution of different etiological factors is as follows:[18,20]

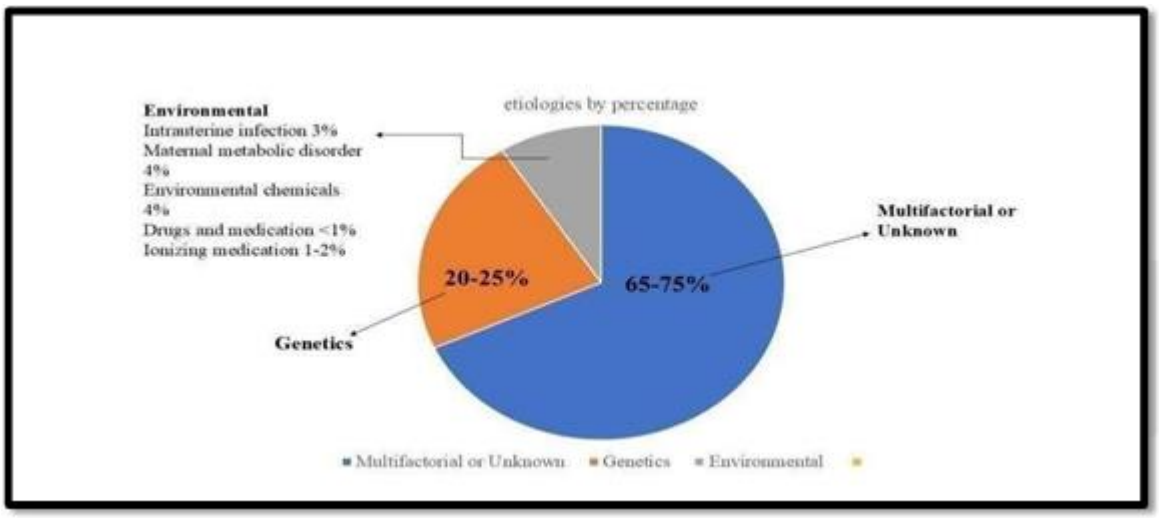

Fig. 2: Percentage Distribution of Etiological Factors in Teratogenesis.

6 WHY TIMING MATTERS: CRITICAL WINDOWS OF DEVELOPMENT

Embryonic and fetal development proceeds through well-defined stages. The timing of exposure to a teratogen is at least as important as the dose or the agent itself

- Pre-implantation (conception to ~2 weeks) — often called the "all-or-none" period: high-dose insults typically cause embryonic loss, while surviving embryos are usually not malformed.
- Embryonic period (approx. Weeks 3–8) — the period of organogenesis and the most sensitive window for structural malformations. Exposure to teratogens during this window commonly produces major congenital anomalies (e.g., limb, cardiac, craniofacial defects).
- Fetal period (approx. Week 9 to term) — continued growth and functional maturation. Teratogenic exposures in this stage tend to cause growth restriction, impaired organ maturation, neurodevelopmental disorders, or functional deficits rather than gross structural malformations.[22,25]

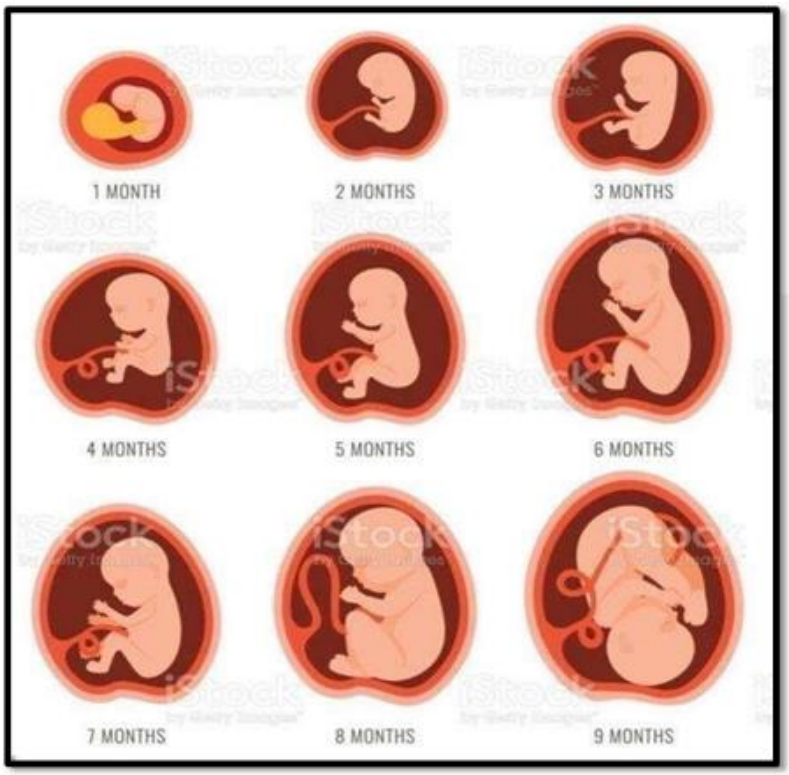

Fig. 3: Timeline of fetal development and critical window.

7 PRINCIPLES OF TERATOLOGY (TRENDING AND UNIQUE PERSPECTIVES)

The study of teratology revolves around understanding how various factors disrupt normal embryonic development and lead to congenital anomalies. Modern research has evolved beyond classical observations and now integrates genomics, epigenetics, molecular signaling, and environmental toxicology to explain how teratogens act. The following are six trending and uniquely redefined principles of teratology that reflect today's scientific understanding.

- **Principle 1: Genetic–Epigenetic Susceptibility**

The response of the embryo to a teratogen is determined by its genetic makeup and epigenetic regulation. Teratogens can alter gene expression through DNA methylation, histone modification, or non-coding RNAs, leading to long-term developmental effects.

Example: Valproic acid modifies histone acetylation, disturbing neural tube formation.

- **Principle 2: Developmental Stage–Dependent Sensitivity**

The timing of exposure defines the type and severity of the defect. During organogenesis (3–8 weeks), structural malformations are most likely, while later exposure may affect function, growth, or neurobehavior.

Example: Thalidomide exposure during limb bud formation leads to phocomelia.

- **Principle 3: Molecular Pathway Interference**

Each teratogen acts through specific cellular and molecular pathways—such as interference with cell signaling, oxidative stress, apoptosis, or angiogenesis.

Example: Isotretinoin disrupts retinoicacid signaling, impairing craniofacial development.

- **Principle 4: Dose, Duration, and Combined Exposure Relationship**

Teratogenic effects follow a dose–response relationship; higher doses or longer exposures cause more severe outcomes. Modern studies also emphasize polyteratogenic exposure, where multiple mild agents together produce significant effects.

Example: Co-exposure to alcohol and nicotine enhances fetal growth restriction.

- **Principle 5: Maternal and Placental Mediation**

Teratogenic effects are influenced by maternal metabolism, placental transfer, and nutritional status. The placenta is not just a barrier but an active modulator of fetal exposure.

Example: Drugs with high lipid solubility like alcohol or isotretinoin cross the placenta easily and affect fetal organs.

- **Principle 6: Spectrum of Developmental Manifestations**

Teratogenesis produces a continuum of outcomes, ranging from cell death to functional or behavioral abnormalities. New technologies like AI-based fetal imaging and

neurodevelopmental biomarkers are improving early detection.

Example: Prenatal exposure to antiepileptic drugs may cause cognitive or behavioral impairments in later childhood.[28,29]

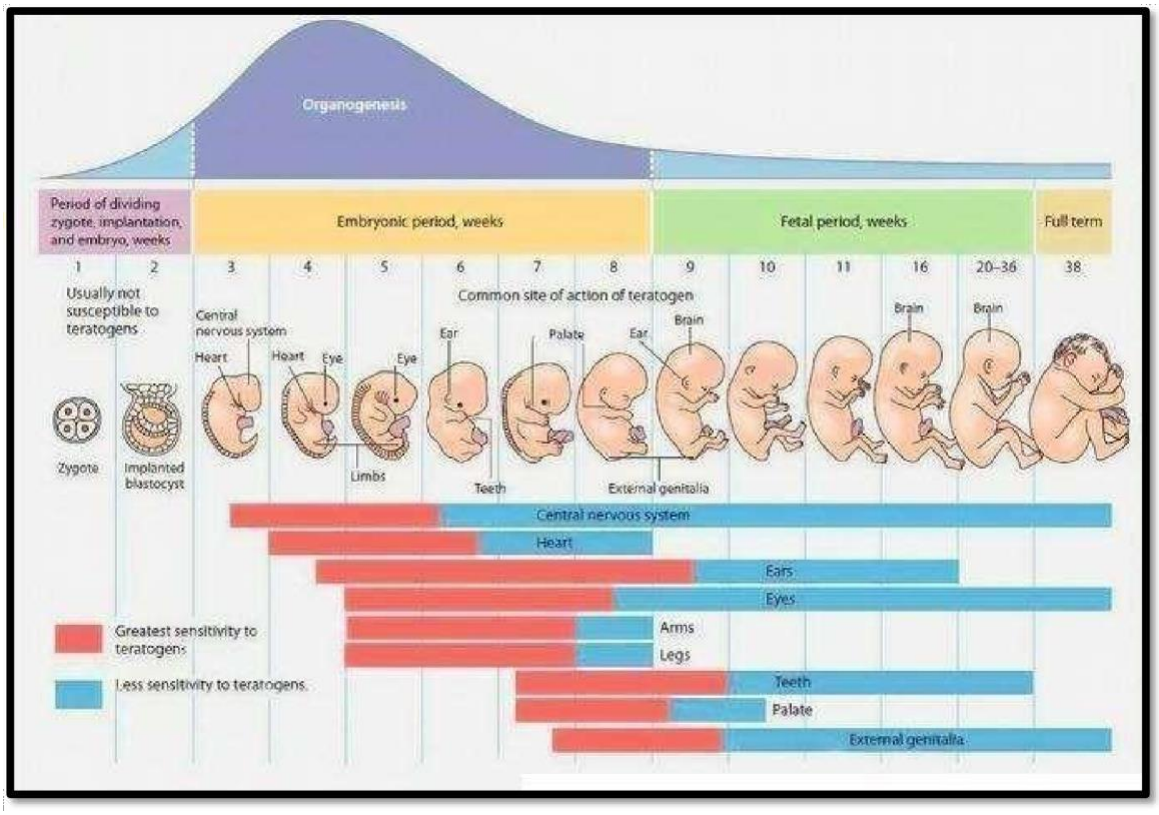

Fig. 4: Sensitivity to teratogens during pregnancy.

8 TERATOGENIC DRUG

1. Lenalidomide
2. Isotretinoin
3. Valproic Acid
4. Methotrexate
5. Misoprostol
6. Warfarin
7. Mycophenolate mofetil
8. Thalidomide
9. Topiramate
10. ACE inhibitors (e.g., Enalapril, Lisinopril).

Table: Teratogenic drug and their effect on fetus.[30,31,32]

Sr.No.	Drug	Effects of Fetus/ Offspring
1.	ACE inhibitor	Foetal loss Growth retardation Renal damage
2.	Anti-cancer drug	Foetal death Hydrocephalus Multiple defects
3.	Aspirin	Premature closure of the ducts arteriosus
4.	Thalidomide	Phocomelia Absence long bone of the limbs Absence of external Multiple defect
5.	Warfarin	Eye and hand defect Growth retardation CNS malformation

9. SELECTED DRUGS KNOWN TO POSE TERATOGENIC RISKS DURING PREGNANCY AND THE SPECIFIC FETAL EFFECTS LINKED TO THEIR EXPOSURE

1. Lenalidomide and Pregnancy

- **Historical Background**

Lenalidomide was developed in the late 1990s as a safer derivative of thalidomide, the drug responsible for the1960s global tragedy of birth defects (phocomelia).

Scientists modified thalidomide's chemical structure hoping to retain its anti-cancer. and immunomodulatory benefits while reducing teratogenicity.

However, animal studies and post-marketing surveillance later confirmed that lenalidomide remains highly teratogenic, with effects similar to or worse than thalidomide in embryonic development.

This led to strict pregnancy prevention programs and REMS (Risk Evaluation and Mitigation Strategy) systems worldwide.

- **Lenalidomide Syndrome**

The term "Lenalidomide Syndrome" refers to the cluster of congenital abnormalities seen in fetuses exposed to lenalidomide in utero — similar to, but distinct from, thalidomide embryopathy.

Typical features include

- Limb reduction defects (shortened or missing limbs)

- Facial anomalies (low-set ears, cleft palate)
- Cardiac defects
- Urogenital malformations

It is considered a modern variant of thalidomide embryopathy, caused by the same Cereblon mediated pathway.

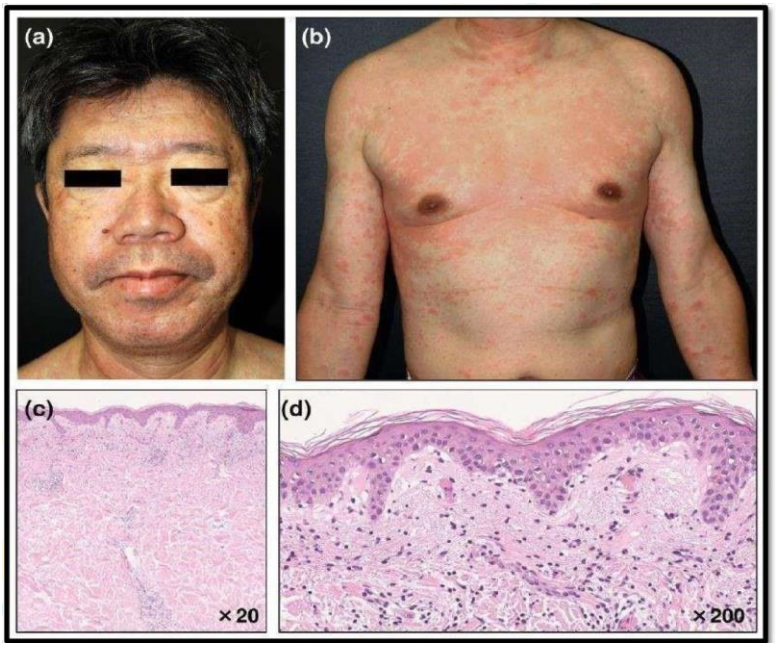

Fig. 5: Lenalidomide syndrome.

2 Isotretinoin and pregnancy

- **Historical background**

1982: Isotretinoin (brand name Accutane) was introduced for severe acne.

Early 1980s: Soon after its approval, reports appeared of infants born with severe congenital malformations when mothers had taken isotretinoin during pregnancy.
1985 onward: Multiple case studies linked isotretinoin with a characteristic pattern of birth defects — termed Isotretinoin Embryopathy or Isotretinoin Syndrome.

As a result, strict pregnancy prevention programs such as iPLEDGE (U.S.) were established to control its use.

- **Isotretinoin Syndrome (Retinoid Embryopathy)**

Isotretinoin Syndrome, also known as Retinoid Embryopathy, refers to a distinct pattern of congenital malformations that occur in fetuses exposed to isotretinoin (a retinoid derivative of

vitamin A) during early pregnancy, particularly during organogenesis (first trimester).

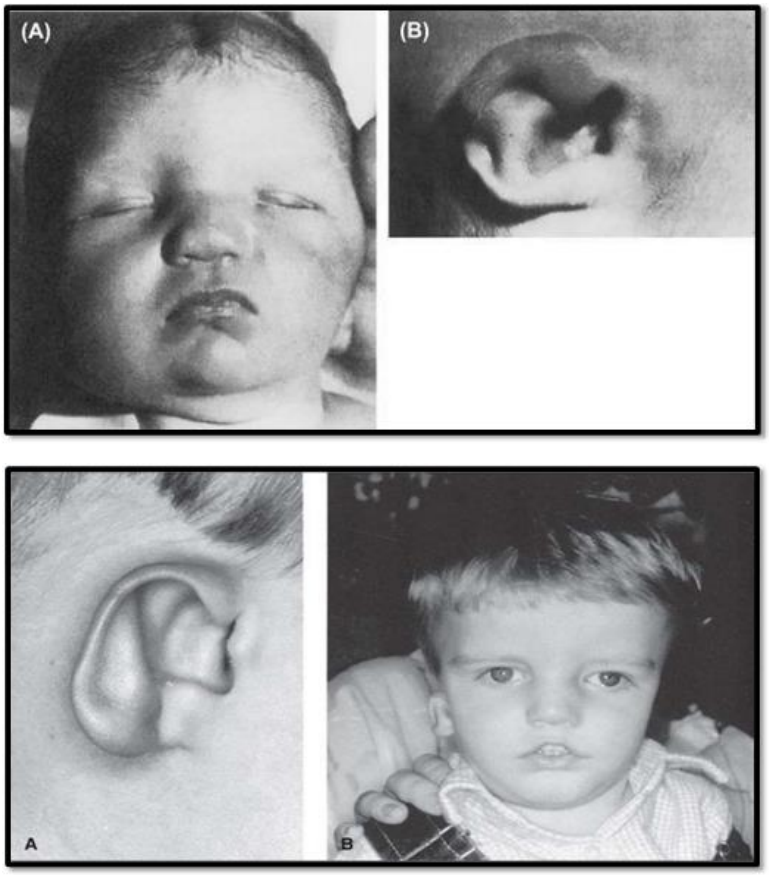

Fig. 6: Isotretinoin Syndrome (Retinoid Embryopathy).

3. Valproic Acid and pregnancy

- **Historical background**

1967: Valproic acid introduced as an antiepileptic agent.

1980s: First reports emerged linking valproic acid use in pregnancy to neural tube defects (NTDs) such as spina bifida.

1990s–2000s: Increasing evidence of developmental delays, autism spectrum disorders, and craniofacial defects in exposed children.

This led to major regulatory warnings and pregnancy prevention programs for women of reproductive age taking valproate.

- **Valproic Acid Syndrome (Fetal Valproate Syndrome)**

Valproic Acid Syndrome (VAS) — also known as Fetal Valproate Syndrome (FVS) — refers to a distinct group of congenital malformations and neurodevelopmental defects that occur in babies born to mothers who took valproic acid during early pregnancy, especially during the

first trimester (3^{rd}–8^{th} week of gestation).

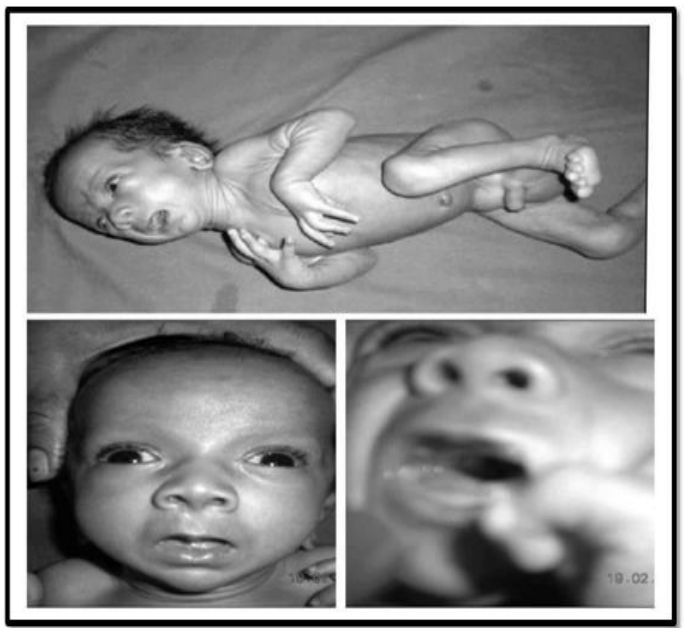

Fig. 7: Valproic Acid Syndrome (Fetal Valproate Syndrome).

4 Methotrexate and pregnancy

- **Historical background**

1940s: Developed as one of the first antifolate chemotherapeutic drugs (by Sidney Farber).

1950s–1960s: Widely used for malignancies and autoimmune diseases.

1970s: Reports emerged of fetal malformations and growth retardation in infants exposed in utero.

1980s: Recognized as a definite human teratogen, leading to classification as Pregnancy Category X.

Today: Use during pregnancy is strictly contraindicated, except for intentional pregnancy termination or ectopic pregnancy management

- **Methotrexate Syndrome (Fetal Methotrexate Syndrome)**

Methotrexate Syndrome, also known as Fetal Methotrexate Syndrome (FMS), refers to a characteristic pattern of congenital malformations, growth restriction, and developmental abnormalities that occur when the fetus is exposed to methotrexate during early pregnancy, particularly during the critical period of organogenesis (6–8 weeks of gestation).

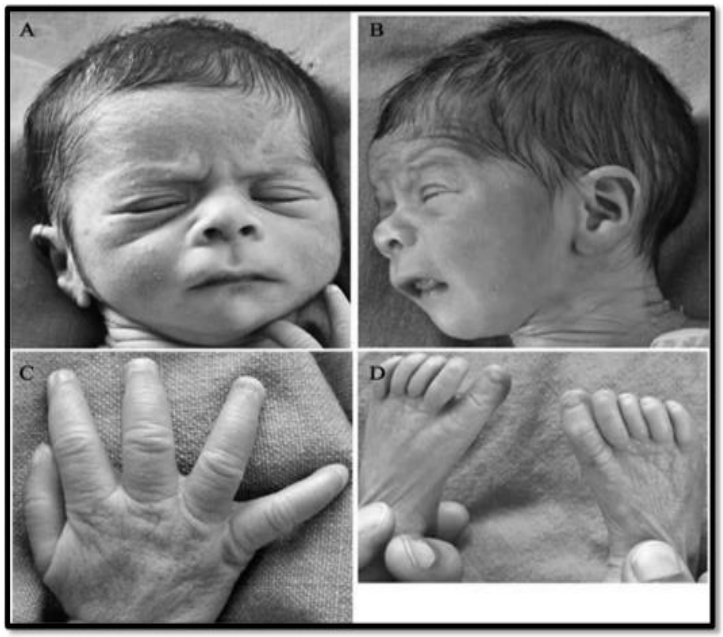

Fig. 8: Methotrexate Syndrome (Fetal Methotrexate Syndrome.

5 Misoprostol and pregnancy

- **Historical background**

1980s: Misoprostol introduced for prevention of NSAID-induced gastric ulcers.

Soon after, it was recognized for its uterotonic property, leading to widespread use in medical abortion.

1990s: Reports emerged from Brazil and Latin America of babies born with congenital anomalies following failed abortion attempts with misoprostol.

This led to the recognition of a distinct pattern of fetal abnormalities called the Misoprostol Syndrome.

- **Misoprostol Syndrome (Fetal Misoprostol Syndrome)**

Misoprostol Syndrome, also known as Fetal Misoprostol Syndrome (FMS), refers to a distinct pattern of congenital malformations that occur when a fetus is exposed to misoprostol during early pregnancy, especially in failed abortion attempts.

The abnormalities arise due to vascular disruption and uterine ischemia rather than direct genetic damage.

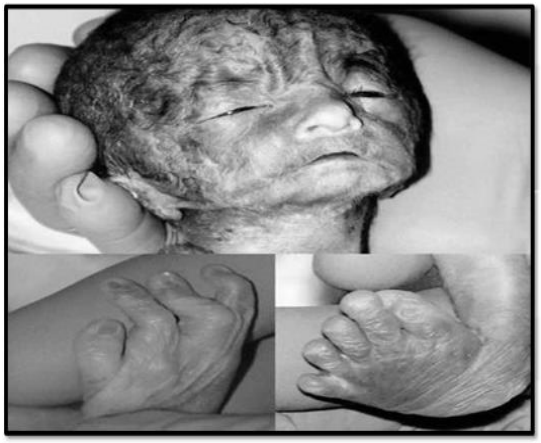

Fig. 9: Misoprostol Syndrome (Fetal Misoprostol Syndrome).

6. Warfarin and pregnancy

- **Historical background**

1940s: Warfarin developed as a rodenticide and later as a therapeutic anticoagulant in humans.

1950s: Reports began emerging of fetal malformations and miscarriages in mothers taking warfarin.

1960s–1970s: Characteristic pattern of defects recognized and named Fetal Warfarin Syndrome (Warfarin Embryopathy).

Since then, strict recommendations have been made to avoid warfarin in pregnancy, especially during the first trimester.

- **Warfarin Syndrome (Fetal Warfarin Syndrome)**

Warfarin Syndrome (FWS) — also called Warfarin Embryopathy — is a congenital malformation syndrome caused by maternal use of warfarin during early pregnancy, typically between the 6^{th} and 12^{th} weeks of gestation.[34,35]

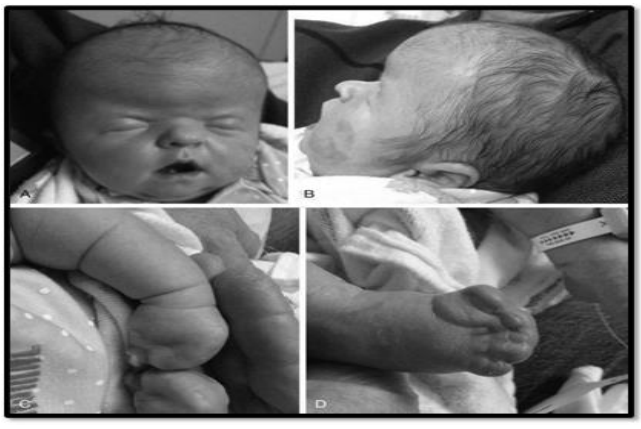

Fig. 10: Warfarin Syndrome (Fetal Warfarin Syndrome).

7. Mycophenolate mofetil and pregnancy

- **Historical background**

1995: Mycophenolate mofetil was approved for clinical use in transplant patients.

Early 2000s: Case reports and registry data began showing increased rates of spontaneous abortions and birth defects among women exposed during pregnancy.

2007: The U.S. FDA issued a black box warning for teratogenicity and mandated a pregnancy prevention program.

These findings led to the recognition of a distinct pattern of birth defects — now termed Mycophenolate Mofetil Embryopathy (MMF Syndrome).

- **Mycophenolate Mofetil Syndrome (Embryopathy)**

Mycophenolate Mofetil Syndrome (MMF Embryopathy) refers to a distinct pattern of congenital malformations seen in fetuses exposed in-utero to Mycophenolate Mofetil (MMF) or its active metabolite Mycophenolic Acid (MPA), especially during the first trimester of pregnancy.

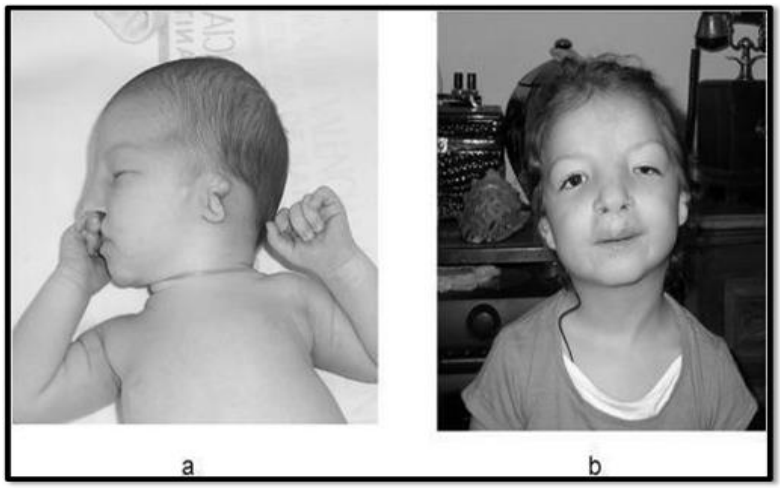

Fig. 11: Mycophenolate Mofetil Syndrome (Embryopathy).

8. Thalidomide And pregnancy

- **Historical background**

1957: Thalidomide was first marketed in West Germany as a safe over-the-counter sedative and anti-nausea drug (brand name Contergan).

1959–1961: Thousands of infants were born with severe limb and organ malformations — a global medical disaster.

1961: Dr. William McBride (Australia) and Dr. Lenz (Germany) identified thalidomide as the

cause of these birth defects.

Following this, thalidomide was withdrawn from the market worldwide.

This tragedy led to the foundation of modern drug regulation and teratology research.

- **Thalidomide Syndrome (Phocomelia or Thalidomide Embryopathy**

Thalidomide Syndrome, also called Thalidomide Embryopathy or Phocomelia, refers to a specific pattern of congenital malformations seen in infants whose mothers took thalidomide during early pregnancy (especially between 20th and 36th day after conception).[35,36]

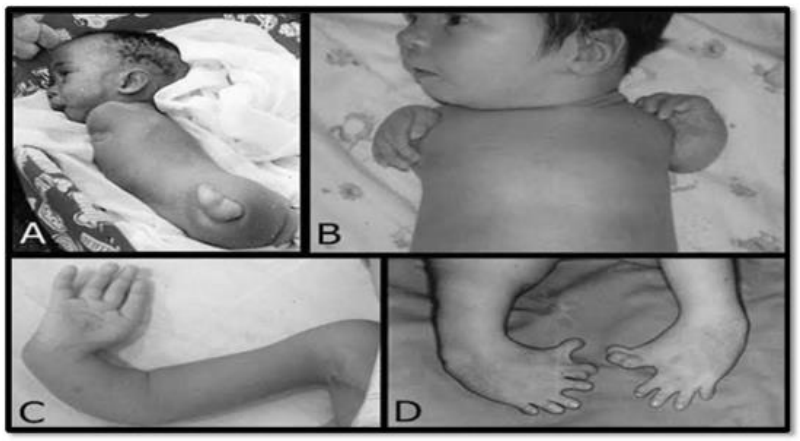

Fig. 12: Thalidomide Syndrome (Phocomelia or Thalidomide Embryopathy.

9. Topiramate and pregnancy

- **Historical background**

1996: Topiramate approved as an anticonvulsant.

Early 2000s: Case reports began linking prenatal exposure to cleft lip and palate.

2011: FDA issued a safety alert confirming increased risk of oral clefts in infants exposed during the first trimester.

Since then, it has been classified as Pregnancy Category D, meaning positive evidence of human fetal risk.

- **Topiramate Syndrome (Fetal Topiramate Syndrome)**

Topiramate Syndrome, also called Fetal Topiramate Syndrome (FTS), refers to a distinct pattern of congenital malformations and developmental abnormalities seen in infants exposed to Topiramate during early pregnancy.

It is categorized as a drug-induced teratogenic syndrome caused by prenatal exposure to the

antiepileptic drug Topiramate.

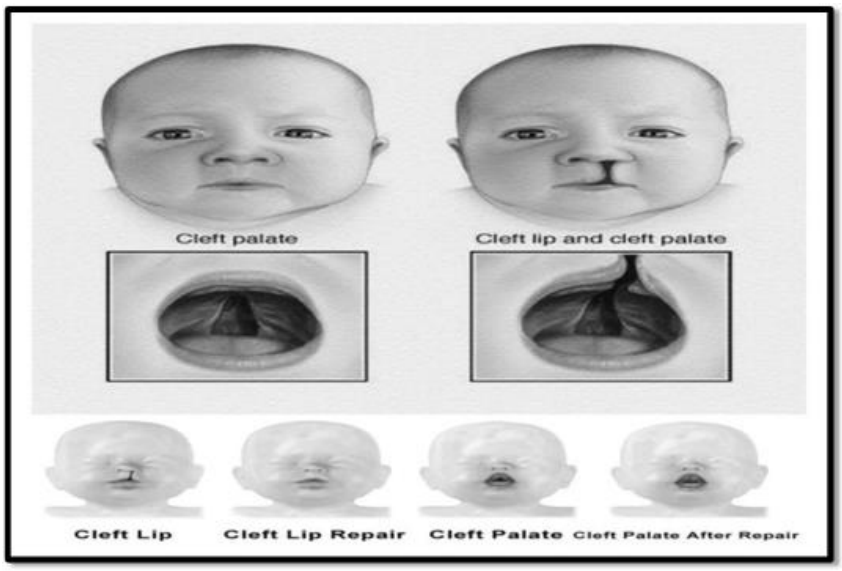

Fig. 13: Topiramate Syndrome (Fetal Topiramate Syndrome).

10. ACE inhibitors (e.g., Enalapril, Lisinopril) and pregnancy

- **Historical background**

1970s: ACE inhibitors were first introduced as antihypertensive drugs.

1980s: Case reports began describing fetal renal failure and skull ossification defects in babies born to mothers taking ACE inhibitors.

1981–1985: Several studies confirmed a clear link between second and third-trimester exposure and fetal toxicity (renal and skeletal abnormalities).

The term "ACE Inhibitor Fetopathy" or "ACE Inhibitor Syndrome" was coined to describe this pattern of defects.

Subsequently, ACE inhibitors were labeled Pregnancy Category D/X, and alternative antihypertensives (like methyldopa or labetalol) were recommended.

- **ACE Inhibitor Syndrome (ACE Inhibitor Fetopathy**)

ACE Inhibitor Syndrome, also known as ACE Inhibitor Fetopathy, refers to a distinct pattern of fetal and neonatal abnormalities that occur when Angiotensin-Converting Enzyme (ACE) inhibitors (e.g., Enalapril, Lisinopril, Captopril) are used by pregnant women — particularly during the second and third trimesters of pregnancy.[37,38]

- **ACE Inhibitor Side Effects**
- Cough
- Angioedema / Agranulocytosis
- Proteinuria / Potassium excess (hyperkalemia)
- Taste change
- Orthostatic hypotension
- Pregnancy contraindication (fetal renal damage)
- Renal artery stenosis contraindication
- Increases renin
- Leukopenia / Liver toxicity

10 MODERN FDA FRAMEWORK FOR EVALUATING DRUG-INDUCED FETAL RISKS ACROSS PREGNANCY STAGES

The U.S. Food and Drug Administration (FDA) plays a key role in evaluating the teratogenic potential of drugs used during pregnancy. Initially, in 1979, the FDA introduced the Pregnancy Risk Category System (A, B, C, D, X) to classify drugs according to fetal risk based on available human and animal studies.[54,55]

Category A: Controlled studies show no fetal risk.

Category B–D: Increasing levels of potential risk; benefits may outweigh harm.

Category X: Proven fetal risk; contraindicated in pregnancy.

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

Although widely used, this letter-based system was criticized for oversimplification and failure to specify timing, severity, or type of developmental toxicity. For instance, certain drugs may cause malformations only during organogenesis (first trimester), yet the category gave no stagespecific information.

To overcome these limitations, the FDA implemented the Pregnancy and Lactation Labeling Rule (PLLR) in 2015, marking a major shift from simple categorization to a datadriven, narrative labeling system. The PLLR provides detailed summaries under three main sections:

1. Pregnancy – includes Risk Summary, Clinical Considerations, and Data sections with information about fetal effects, timing of exposure, and dose-related outcomes.
2. Lactation – addresses excretion of the drug into breast milk and potential infant effects.
3. Reproductive Potential – includes information on contraception, fertility, and pre-pregnancy testing.[56,57]

Current Trends and Level of Evidence

- Modern FDA labeling emphasizes trimester-specific risk assessment by integrating human clinical data, animal studies, and post-marketing surveillance.
- Studies show that around 89–90% of labels still rely mainly on animal data, while only 10–12% include human pregnancy data, indicating a need for stronger evidence sources.
- The FDA now encourages data from Pregnancy Exposure Registries and Real World Evidence (RWE) to improve understanding of stage-dependent teratogenic effects.
- Integration of Artificial Intelligence (AI) and machine learning tools helps identify hidden patterns of fetal risk from large health databases.
- Continuous updates of labeling information ensure dynamic risk communication, aligning with global trends in evidence-based pharmacovigilance.

Significance

The PLLR framework supports individualized risk evaluation, linking teratogenic outcomes with the specific developmental stage at which drug exposure occurs. This evolution reflects a global shift toward precision teratology, promoting safer prescribing practices and improved protection of maternal and fetal health.[61,62]

11. PREVENTION AND CONTROL OF TERATOGENESIS

The prevention and control of teratogenesis focus on reducing the risk of congenital malformations by eliminating or minimizing exposure to teratogenic factors during critical

stages of fetal development. Current strategies emphasize preconceptional planning, where genetic counseling, control of chronic maternal diseases, and folic acid supplementation play vital roles in preventing neural tube and other birth defects. During pregnancy, rational drug use, avoidance of alcohol, tobacco, and radiation, and adoption of a balanced diet free from high-mercury foods are strongly recommended. Regular prenatal screening and ultrasonographic monitoring help in early detection of anomalies, allowing timely medical intervention. From a regulatory perspective, the FDA's Pregnancy and Lactation Labeling Rule (PLLR) has replaced the traditional A–X categories, providing detailed risk–benefit information for drug use in pregnancy. Additionally, pharmacovigilance systems, public awareness campaigns, and environmental safety measures are key components of modern preventive practice. Emerging trends include the development of non-teratogenic and targeted drug delivery systems, in-vitro and AIbased teratogenicity prediction models, and genomic screening to identify individual susceptibility to teratogens. Collectively, these evolving strategies reflect a proactive, technology-driven approach to safeguarding maternal and fetal health in the current era.[62,63,64]

20. AYURVEDIC FORMULATIONS AND PREGNANCY: SAFETY CONSIDERATIONS IN THE CONTEXT OF TERATOGENICITY

Ayurvedic medicine has traditionally described several herbal and herbo-mineral formulations for supporting maternal health and fetal growth. Preparations such as Madeephalarasayana, Sindurabhushanam, and Swarnamalinivasantarasa are commonly referenced in classical texts for improving digestion, strength, immunity, and pregnancy outcomes. Although these formulations hold cultural and therapeutic significance, their safety in pregnancy remains poorly established in the context of modern teratology.

Many Ayurvedic rasayana and rasoushadhi preparations contain processed metals or minerals (e.g., gold, mercury, sulfur, or other bhasmas). When properly purified according to traditional methods (shodhana and marana), these substances are claimed to be safe; however, variability in manufacturing, lack of standardization, and potential contamination raise concerns. The first trimester (especially 3–8 weeks) represents the critical window of organogenesis, during which the fetus is highly sensitive to toxic exposures. Therefore, any product containing heavy metals, impurities, or unregulated ingredients may pose a theoretical risk of teratogenicity, growth restriction, or developmental delay.

Current scientific evidence regarding the teratogenic or fetotoxic effects of these specific formulations is extremely limited, and controlled clinical trials in pregnant women are lacking. Most available data are based on traditional practice, anecdotal use, or small observational studies that do not provide conclusive safety assurance. As a result, the use of complex herbo- mineral Ayurvedic preparations during pregnancy should be undertaken only under the supervision of trained practitioners, and commercial/unregulated products should be avoided.

Overall, while Ayurvedic formulations have a long history of use in pregnancy-related conditions, their teratogenic risk cannot be fully ruled out without systematic toxicological and clinical evaluation. More research especially developmental toxicity studies, standardization protocols, and pregnancy safety trials is required to clarify their safety profile during critical stages of fetal development.[65,66]

Madeephalarasayana

Madeephalarasayana is a classical Ayurvedic preparation traditionally prescribed for pregnancyrelated nausea, vomiting (garbhini chhardi), and digestive discomfort. It is considered a rasayana that supports maternal digestive strength and reduces acidity

- **Ingredient**

Madiphala (acidic fruit-based extract, often Citrus species) Madhuka (Glycyrrhiza glabra licorice)
Pippali (Piper longum)
Dhanyaka (Coriandrum sativum)
Ghee or honey as anupana

- **Dose**:- 5–10 mL daily (as mentioned in classical usage; not an evidence-based clinical dose)

Fig. 14: Madeephalarasayana.[68]

Sindurabhushanam

Sindurabhushanam is an Ayurvedic herbo-mineral formulation traditionally used for nausea, vomiting, burning sensation, and discomfort during pregnancy. It is considered potent due to the presence of bhasma and sindura preparations.

- **Ingredient**

Abhrakabhasma (Sataputa) – purified mica

Rasa Sindura – processed mercurial compound Suddha Gandhaka – purified sulfur

Suddha Tankana – purified borax

- **Dose**:- 1 g × 4 doses daily, mixed with dried jeeraka (cumin) powder Taken with Madeephalarasayana or Draksharishta as adjuvant

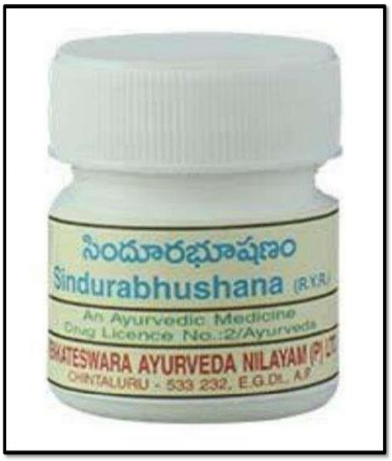

Fig. 15: Sindurabhushanam.[69]

13. CONCLUSION

Teratogenicity remains a critical concern in maternal and fetal health, as drug exposure during pregnancy can result in structural or functional abnormalities depending on the timing, dosage, and nature of the drug. The susceptibility of the developing embryo or fetus varies with each stage of pregnancy ranging from implantation loss in the preembryonic stage to major organ malformations during organogenesis, and functional impairments in the fetal period. Understanding these stage-specific effects is essential for safe pharmacotherapy. Recent advancements such as the FDA Pregnancy and Lactation Labeling Rule (PLLR), genetic and molecular screening, and pharmacovigilance programs have improved awareness and safety in clinical practice. Moreover, the development of targeted and biodegradable drug delivery systems offers promising approaches to minimize fetal exposure while maintaining maternal efficacy. Overall, effective prevention of teratogenic effects requires a multidisciplinary approach, combining clinical judgment, patient education, and ongoing research to ensure safe and evidence-based drug use during pregnancy.[70,71,72]

14. REFRENCES

1. International Journal of Creative Research Thoughts (IJCRT), Volume 12, Issue 4, 2024. https://ijcrt.org/papers/IJCRT2310315.pdf
2. Pramanick, A., Roy, I., Datta, A., Dewan, S., & Vandana. (2023). Teratogenic effect of drugs at different stages of pregnancy. IJPSR. https://ijpsr.com/bft-article/teratogenic-effect-of- drugs-at-different-stages-of-pregnancy/
3. Alwan, S., & Grant, K. S. (2024). Maternal medication use in pregnancy: Assessing and communicating the “risk” of birth defects. Pharmacoepidemiology. https://www.mdpi.com/2813-0618/3/4/23
4. The Teratology Society. (2017). Timeline of important events during pregnancy andteratogenic exposure. https://www.birthdefectsresearch.org/primer/PrimerPDF/What-Is-the-Timeline-of-Important-Events-During-Pregnancy-That-May-Be-Disrupted-by-a-Teratogenic-Exposure.pdf
5. Luke D Starling, 1 Ashutosh Sinha, 2 Duncan Boyd, 3 and Anke Furck Fetal warfarin sy Alwan S, Polifka JE, Friedman JM. B. Addendum: Sartan treatment during pregnancy. Birth Defects Res a Clin Mol Teratol, 2005; 73: 904–905.
6. 3. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Roblin D, Smith DH, Yood MU, Morse AN, Platt R. 2004. Prescription drug use in pregnancy. Am J Obstet Gynecol, 2004; 191: 398–407.

7. Punam Sachdeva, B. G. Patel, and B. K. Patel1 Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb
8. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester.
9. Vargesson, Neil and Fraga, Lucas (December 2017) Teratogenesis. In: eLS. John Wiley & Sons, Ltd: Chichester. DOI: 10.1002/9780470015902.a0026056.
10. Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 1999 Feb; 19(2): 221-2.5. Burrow GN. Thyroid function and hyperfunction during gestation. Endocrine Reviews. 1993 Apr 1; 14(2): 194-202.
11. Mastroiacovo P, Mazzone T, Botto LD, Serafini MA, Finardi A, Caramelli L, Fusco D. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. American journal of obstetrics and gynecology, 1996 Dec 1; 175(6): 1645-50.
12. Jamkhande, P. G., Chintawar, K. D., & Chandak, P. G. (2014). Teratogenicity: A mechanism- based short review on common teratogenic agents. Asian Pacific Journal of Tropical Disease, 4(6): 421-432. DOI: 10.1016/S2222-1808(14)60600-9.
13. Pramanick, A., Roy, I., Datta, A., Dewan, S., & Vandana. (2023). Teratogenic effect of drugs at different stages of pregnancy. International Journal of Pharmaceutical Sciences and Research, 14(11): 5380-5389.
14. Hale F. The relation of vitamin A to anophthalmos in pigs. American Journal of Ophthalmology, 1935 Dec 1; 18(12): 1087-93.
15. Warkany J, Schraffenberger E. Congenital malformations of the eyes induced in rats by maternal vitamin A deficiency. Proceedings of the Society for Experimental Biology and Medicine, 1944 Oct; 57(1): 49-52.
16. WARKANY J. Effect of maternal rachitogenic diet on skeletal development of young rat. American Journal of Diseases of Children, 1943 Nov 1; 66(5): 511-6.
17. 15. Fonseca W, Alencar AJ, Pereira RM, Misago C. Congenital malformation of the scalp and cranium after failed first trimester abortion attempt with misoprostol. Clinical Dysmorphology, 1993 Jan 1; 2(1): 76-80.
18. Gonzalez CH, Vargas FR, Perez AB, Kim CA, Brunoni D, Marques-Dias MJ, Leone CR, Neto JC, Llerena Jr JC, de Almeida JC. Limb deficiency with or without Möbius sequence in seven Brazilian children associated with misoprostol use in the first trimester of pregnancy. American Journal of Medical Genetics, 1993 Aug 1; 47(1): 59-64.

19. Castilla EE, Orioli IM. Teratogenicity of misoprostol: data from the Latin-American collaborative study of congenital malformations (ECLAMC). American journal of medical genetics, 1994 Jun 1; 51(2): 161-2.
20. DR G. Limb defects and omphalocele in a 17-week fetus following first trimester misoprostol exposure. Teratology, 1994; 49: 418.
21. Vargas FR, Brunoni D, Gonzalez C, Kim C, Meloni V, Conte A. Investigation of the teratogenic potential of misoprostol. Teratology, 1997; 55: 104.
22. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. New England journal of medicine, 2000 Nov 30; 343(22): 1608-14
23. Hayes TB, Anderson LL, Beasley VR, De Solla SR, Iguchi T, Ingraham H, Kestemont P, Kniewald J, Kniewald Z, Langlois VS, Luque EH. Demasculinization and feminization of male gonads by atrazine: consistent effects across vertebrate classes. The Journal of steroid biochemistry and molecular biology, 2011 Oct 1; 127(1-2): 64-73.
24. Risk and Benefit of Drug Use During Pregnancy Ferenc Bánhidy, 1 R.Brian Lowry, 2 and Andrew 10.7150/ijms.2.100 E. Czeizel3. DOI: PMCID: PMC1168874PMID: 16007261.
25. Punam Sachdeva, B.G.Patel and B.K.Patel' Drug use in pregnancy a point to ponder! 2009 Jan-Feb. 3. Michelle L. Myer, DNP, RN, APRN, CPNP, Dr. Leon Bullard, and Dr. V. Leigh Beasley, Department of Health and Environmental Control; and Danielle Gentile, Ph.D. Candidate, Arnold School of Public Health, University of South Carolina
26. Michelle L. Myer, DNP, RN, APRN, CPNP, Dr. Leon Bullard, and Dr. V. Leigh Beasley, Department of Health and Environmental Control; and Danielle Gentile, Ph.D. Candidate, Arnold School of Public Health, University of South Carolina.
27. Teratogenic Effect of Different Drug at Different Stages of Pregnancy by Pranali Patil, Ashwini Patil, Mr.Siddheshwar Mahesh Shinde, Ankita Nanaware. ISSN:2349-5162, Mohite, Ms Vol.9, Issue 12, page no. Ppa152-a161, December 2022; Available at http://www.jetir.org/papers/JETIR2212018.pd f. 5.
28. Luke D Starling, 1 Ashutosh Sinha, 2 Duncan Boyd, 3 and Anke Furck Fetal warfarin sy Alwan S, Polifka JE, Friedman JM. B. Addendum: Sartan treatment during pregnancy. Birth Defects Res a Clin Mol Teratol, 2005; 73: 904–905.
29. Alwan S, Polifka JE, Friedman JM. A. Angiotensin II receptor antagonist treatment during pregnancy. Birth Defects Res a Clin Mol Teratol, 2005; 73: 123–130.
30. Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Roblin D, Smith DH, Yood MU, Morse AN, Platt R. 2004. Prescription drug

use in pregnancy. Am J Obstet Gynecol, 2004; 191: 398–407.

31. Punam Sachdeva, B. G. Patel, and B. K. Patel1 Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb.
32. Wilson JG. Current status of teratology. General principles and mechanisms derived from animal studies. In: Handbook of teratology. New York, NY: Plenum Press, 1977; 1: 47-58.
33. Błaszczyk B, Miziak B, Pluta R and Czuczwar SJ: Epilepsy in pregnancy-management principles and focus on valproate. International Journal of Molecular Sciences, 2022; 23(3): 1369.
34. Hansen JM, Harris C. A novel hypothesis for thalidomide-induced limb teratogenesis: redox misregulation of the NF-kB pathway. Antioxid Redox Signal, 2004; 6: 1–14.
35. Songmen S, Panta OB, Paudel SS and Ghimire RK: Chondrodysplasia punctata: A Case Report of Fetal Warfarin Syndrome. Journal of Nepal Health Research Council, 2017; 15(1): 81-84.
36. Finnell RH, Dansky LV. Parental epilepsy, anticonvulsant drugs and reproductive outcome: epidemiological and experimental findings spanning three decades. I. Animal studies. Reprod Toxicol, 1991; 5: 281-299.
37. Dansky LV, Finnell RH. Parental epilepsy, anticonvulsant drugs andreproductive outcome: epidemiological and experimental findings spanning three decades. II. Human studies. Reprod Toxicol, 1991; 5: 281-298. 13.
38. 13 Stacy Mosel, L.M.S.W.: Sco Thomas, MD Dangers of Using Cocaine During Pregnancy, Sep 14; 2022.
39. Henkel L, Willert HE. Dysmelia: a classification and pattern of malformation in a group of congenital defects of the limbs. J Bone Joint Surg, 1969; 51B: 399.
40. McCredie J. Embryonic neuropathy: a hypothesis of neural crest injury as the pathogenesis of congenital malformations. Med J Aust., 1974; 1: 159–163.
41. McCredie JM. Comments on ―Proposed mechanisms of action in thalidomide embryopathy.‖ Teratology, 1990; 41: 239–242.
42. McCredie J, North K, de Iongh R. Thalidomide deformities and their nerve supply. J Anat., 1984; 139: 397–410.
43. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. PNAS USA., 1994; 91: 4082–4085.
44. Friedman JM. Effects of drugs and other chemicals on fetal growth. Growth Genet., 1992; 8: 1– 5.

45. Cregler LL, Mark H. Medical complications of cocaine abuse. NEJM., 1986; 315: 149.
46. Hodach RJ, Hodach AE, Fallon JE, Folts JD, Bruyere HJ, Gilbert EF. The role of betaadrenergic activity in the production of cardiac and aortic arch anomalies in the chick embryo. Teratology, 1975; 12: 33–45.
47. Little BB. Cocaine Abuse during pregnancy: maternal and fetal implications. Obstet Gynecol., 1989; 73: 157–160.
48. Volpe JJ. Mechanisms of disease: effect of cocaine use on the fetus. NEJM, 1992; 327: 399– 407.
49. Herman GE. Disorders of cholesterol biosynthesis: prototypic metabolic malformation syndromes. Hum Mol Genet, 2003; 50.12: 75–88.
50. Porter FD. Human malformation syndromes due to inborn errors of cholesterol synthesis. CurrOpinPediatr, 2003; 15: 607–613.
51. Hayes A, Gilbert A, Lopez G, Miller WA. Mevacor: a new teratogen? Am J Hum Genet., 1995; 57(suppl 4): A92.
52. Thalidomide Teratogenic Effects Linked to Degradation of SALL4: After 60 years, researchers have now shed light on the mechanism underlying thalidomide's devastating teratogenic effects. Am J Med Genet A., 2018 Dec; 176(12): 2538-2539.
53. Thalidomide: Lenz W. Teratogenicity of Thalidomide: A Reassessment. Proc R Soc Med., 1962 Nov; 55(11): 943-6. PMID: 13960254
54. Human reproduction updated volume 16, no. 4PP, 378-394 2010. 6. Stages of Development of the Fetus – Women's Health Issues – MSD Manual Consumer Version (msdmanuals.com).
55. Stages of Development of the Fetus – Women's Health Issues – MSD Manual Consumer Version (msdmanuals.com).
56. Khajekar, A.D., Aher, A.P., Salunke, G.V., & Kawade, R.M. (2023). Teratogenic Effect of Various Medication During Various Phases of Pregnancy. International Journal in Pharmaceutical Sciences, 1(12): 1-13. DOI: 10.5281/zenodo.10245751.
57. Sharma, R., Kesharwani, D., Mishra, S., & Kumari, M. (2023). A Review on Teratogenesis: Current Perspective. International Journal of Pharmaceutical Sciences Review and Research, 82(1): 105–111. DOI: 10.47583/ ijpsrr. 2023.v82i01.017
58. Chung, W. (2004). Teratogens and their effects. Columbia University. Retrieved from https://www.columbia.edu/itc/hs/medical/humandev/2004/Chpt23-Teratogens.pdf.
59. Australas J Ultrasound Med. The development, structure and blood flow within the umbilical cord with particular reference to the venous system.

60. Tan C.M.J. · Lewandowski A.J. the Transitional Heart: From Early Embryonic and Fetal Development to Neonatal Life Ther 2020.
61. Dae D. Chung, Marisa R. Pinson, Lokeshwar S. Bhenderu, Michael S. Lai, Rhea A. Patel, and Rajesh C. Miranda* Toxic and Teratogenic Effects of Prenatal Alcohol Exposure on Fetal Development, Adolescence, and Adulthood Aug; 22.
62. M H Kaufman 1the teratogenic effects of alcohol following exposure during pregnancy, and its influence on the chromosome constitution of the pre-ovulatory egg 1997 Mar-Apr
63. Keshav K. Gupta, Vinay K. Gupta, and Tomohiro Shirasaka an Update on Fetal Alcohol Syndrome—Pathogenesis, Risks, and Treatment Auuest 2016.
64. Basil J. Zitelli MD, in Zitelli and Davis' Atlas of Pediatric Physical Diagnosis, Genetic Disorders and Dysmorphic Conditions, 2018.
65. Appolinary Kamuhabwa and Rashida Jalal Drug use in pregnancy: Knowledge of drug dispensers and pregnant women in Dar as Salaam, Tanzania 2011 May-Jun Punam Sachdeva, * B. G. Patel, and B. K. Patel1 Drug Use in Pregnancy; a Point to Ponder! 2009 Jan-Feb.
66. Brittney D Bastow, MD; Chief Editor: Christine Isaacs, MD Teratology and Drug Use during Pregnancy Nov 09, 2022.
67. Dae D. Chung, Marisa R. Pinson, Lokeshwar S. Bhenderu, Michael S. Lai, Rhea A. Patel, and Rajesh C. Miranda* Toxic and Teratogenic Effects of Prenatal Alcohol Exposure on Fetal Development, Adolescence, and Adulthood.
68. Figure 14 https://images.app.goo.gl/ELryBog8N5RuCbZp8
69. Figure 15 https://images.app.goo.gl/ywsL47cByihzAyr17
70. Brent, R.L. (2004). Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing With These Complex Clinical Problems Caused by a Multitude of Environmental and Genetic Factors. Pediatrics, 113(Supplement_3): 957– 968. https://publications.aap.org/pediatrics/article/113/Supplement_3/957/70119
71. Organization of Teratology Information Specialists (OTIS). What Is the Timeline of Important Events During Pregnancy That May Be Disrupted by a Teratogenic Exposure? https://www.birthdefectsresearch.org/primer/PrimerPDF/What-Is-the-Timeline-of-Important-Events-During-Pregnancy-That-May-Be-Disrupted-by-a-Teratogenic-Exposure.pdf
72. Kennedy, D., & Uhl, K. (2020). Medication Use in Pregnancy: A Maternal–Fetal Safety Perspective. Clinical Obstetrics and Gynecology, 63(1): 134–150. https://journals.lww.com/clinicalobgyn/Fulltext/2020/03000/Medication_Use_in_Pregnanc

y A_Maternal_Fetal.14.asp