ISSN: 2306-6091

International Journal of Pharmaceuticals and Health Care Research (IJPHR)

IJPHR |Vol.14 | Issue 3 | Jul - Sep -2026

www.ijphr.com

DOI : https://doi.org/10.61096/ijphr.v14.iss3.2026.544-557

Teratogenic Effects of Pharmaceuticals During Pregnancy: A Comprehensive Review

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Published on: 17.08.2026

Published by: Futuristic Publications

Abstract: Teratogenicity refers to the ability of certain pharmaceutical agents, chemicals, or environmental factors to interfere with normal embryonic and fetal development resulting in congenital malformations, functional impairments, growth restriction or fetal death. Medication use during pregnancy is common because many women require treatment for acute or chronic medical conditions such as epilepsy, hypertension, diabetes, autoimmune diseases, infections and psychiatric disorders. However, the safety of many medications during pregnancy remains a significant clinical challenge due to physiological changes in the mother, placental drug transfer and the varying susceptibility of the developing fetus at different stages of gestation. Drug exposure during the first trimester, particularly during organogenesis is associated with the highest risk of structural congenital anomalies, whereas exposure during later stages of pregnancy may result in functional abnormalities, impaired fetal growth, or neonatal toxicity. This review provides a comprehensive overview of pharmaceutical teratogenicity, including the biological mechanisms underlying drug-induced congenital anomalies, critical periods of fetal development, placental drug transfer and factors influencing fetal susceptibility. The review discusses major teratogenic medications including antiepileptic drugs, retinoids, antimetabolites, anticoagulants, antihypertensive agents, immunosuppressants and non-steroidal anti-inflammatory drugs with emphasis on their mechanisms of action, teratogenic effects, clinical evidence and recommended risk reduction strategies. Recent advances in pharmacovigilance, pregnancy exposure registries, regulatory frameworks and personalized medicine are also highlighted. In addition, the review emphasizes the importance of preconception counseling, evidence-based prescribing, multidisciplinary collaboration, patient education and continuous fetal monitoring to minimize preventable adverse pregnancy outcomes. Understanding the teratogenic potential of pharmaceuticals is essential for healthcare professionals to balance maternal therapeutic needs with fetal safety. Continuous research improved regulatory guidance and strengthened pharmacovigilance systems are expected to enhance medication safety during pregnancy and contribute to better maternal and neonatal health outcomes.

Keywords: Teratogenicity, Teratogenic drugs; Pregnancy; Congenital anomalies; Birth defects; Drug safety during pregnancy; Fetal toxicity; Valproic

acid pregnancy; Isotretinoin teratogenicity; Methotrexate pregnancy; Warfarin embryopathy; ACE inhibitors pregnancy; NSAIDs pregnancy; Mycophenolate pregnancy; Pharmacovigilance in pregnancy; Placental transfer; Fetal development; Pharmacovigilance; Pregnancy and Lactation Labeling Rule (PLLR); Maternal health; Medication safety.

INTRODUCTION

Teratogenicity refers to the ability of an external agent to interfere with normal embryonic or fetal development, resulting in structural malformations, functional impairments, growth restriction, pregnancy loss, or developmental abnormalities. Agents capable of producing these adverse effects are known as teratogens and include pharmaceutical drugs, environmental chemicals, infectious organisms, radiation, alcohol and certain maternal medical conditions. Among these pharmaceutical agents are of particular concern because medications are frequently required during pregnancy to manage acute and chronic maternal illnesses. While many medicines improve maternal health and pregnancy outcomes, some drugs may cross the placenta and adversely affect fetal development if used during critical stages of gestation.

Congenital anomalies, also known as birth defects are a major public health problem worldwide. According to the World Health Organization (WHO) approximately 240,000 newborns die within the first 28 days of life each year because of congenital anomalies, while many surviving children experience lifelong physical disabilities, developmental delays, or chronic medical conditions. Congenital anomalies contribute substantially to infant mortality, childhood disability, emotional distress among families and increased healthcare costs. Although genetic abnormalities account for many cases, environmental exposures, including certain medications play an important and potentially preventable role in their development.

The relationship between medications and fetal abnormalities became widely recognized following the thalidomide tragedy in the late 1950s and early 1960s. Thalidomide was prescribed to pregnant women for nausea and insomnia but was later found to cause severe limb reduction defects (phocomelia) and other congenital malformations in thousands of infants worldwide. This event transformed drug regulation, emphasizing the need for rigorous developmental toxicity testing, post-marketing surveillance and stricter prescribing practices during pregnancy.

Drug-induced teratogenicity depends on several interacting factors rather than exposure alone. These include the timing of exposure during pregnancy, drug dose, duration of treatment, placental transfer, maternal health status and genetic susceptibility of both the mother and fetus. The period of organogenesis (approximately weeks 3 to 8 after conception) is particularly vulnerable because the major organs are forming during this stage. Exposure to known teratogens during this critical period may result in irreversible structural malformations, whereas exposure later in pregnancy is more likely to affect fetal growth and functional development.

Despite increasing knowledge of medication safety, prescribing medicines during pregnancy remains challenging. Pregnant women are often excluded from clinical trials because of ethical considerations, resulting in limited safety information before new medicines become available. Consequently, much of the current evidence is derived from observational studies, pregnancy exposure registries, pharmacovigilance systems and post-marketing surveillance. These data sources play a crucial role in identifying previously unrecognized fetal risks and guiding evidence based clinical decision making.

Healthcare professionals, including physicians, pharmacists, nurses, clinical pharmacologists and clinical researchers play a key role in minimizing teratogenic risk through preconception counseling, careful medication review, patient education, pharmacovigilance and multidisciplinary collaboration. Recent advances in pharmacogenomics, artificial intelligence, placenta-on-a-chip technology, human organoids and real-world pharmacovigilance databases are improving the understanding and prediction of teratogenic risks. These innovations may enhance medication safety during pregnancy by enabling more personalized treatment decisions and earlier identification of drug-related fetal adverse effects.

This review aims to provide a comprehensive overview of the teratogenic effects of pharmaceuticals during pregnancy. It discusses the mechanisms of teratogenicity, critical periods of fetal

susceptibility, major teratogenic medications, pharmacovigilance strategies, preventive measures and emerging research, thereby supporting evidence-based prescribing and promoting safer maternal and fetal healthcare.

History of Teratogenicity: Past, Present and Future Perspectives:

The concept of teratogenicity has evolved significantly over the past century, transforming from a poorly understood phenomenon into a major area of research in pharmacology, toxicology, developmental biology and maternal-fetal medicine.

A major turning point in the history of teratology occurred during the late 1950s and early 1960s with the thalidomide disaster. Thalidomide was initially introduced as a sedative and was widely prescribed to pregnant women for the treatment of morning sickness because it was believed to be remarkably safe. However, thousands of infants were subsequently born with severe congenital malformations, particularly phocomelia a condition characterized by severely shortened or absent limbs. In addition to limb defects affected infants exhibited abnormalities involving the heart, ears, eyes, kidneys and gastrointestinal tract. It was later established that exposure to thalidomide during the critical period of organogenesis, particularly between the twentieth and thirty-sixth day after fertilization, resulted in irreversible developmental abnormalities. This tragedy highlighted the devastating consequences of inadequate drug testing during pregnancy and fundamentally changed the global approach to drug regulation and reproductive safety evaluation.

Following the thalidomide incident governments and regulatory authorities introduced stringent requirements for preclinical reproductive toxicity testing before the approval of new pharmaceutical products. Animal studies assessing fertility, embryonic development, fetal growth and postnatal development became mandatory components of drug development programs. Regulatory agencies also strengthened pharmacovigilance systems to monitor adverse pregnancy outcomes after medicines entered the market. These measures greatly improved the identification and prevention of drug-induced congenital anomalies.

During the present era, the understanding of teratogenicity has expanded beyond pharmaceuticals to include environmental chemicals, industrial pollutants, radiation, infectious diseases, nutritional deficiencies, maternal illnesses and lifestyle-related factors such as alcohol consumption, tobacco smoking and illicit drug abuse. Research has demonstrated that fetal susceptibility to teratogenic agents depends on multiple interacting factors, including the timing of exposure, dosage, duration of exposure, maternal metabolism, placental drug transfer and genetic susceptibility of both the mother and fetus. Modern healthcare emphasizes individualized risk-benefit assessment before prescribing medications during pregnancy, recognizing that untreated maternal disease may itself pose substantial risks to fetal development.

Regulatory policies have also evolved considerably in recent years. The traditional United States Food and Drug Administration (FDA) pregnancy risk categories (A, B, C, Dand X) which often oversimplified drug safety information have been replaced by the Pregnancy and Lactation Labeling Rule (PLLR). This revised system provides detailed evidence regarding maternal risk, fetal risk, clinical considerations and available human and animal data, enabling healthcare professionals to make more informed therapeutic decisions. Similarly, international organizations continue to strengthen guidelines for pregnancy safety monitoring through pregnancy exposure registries, observational studies and global pharmacovigilance networks.

The future of teratogenicity research is expected to be driven by rapid advances in biomedical science and digital technology. Artificial intelligence and machine learning algorithms are increasingly being developed to predict teratogenic potential based on chemical structure and biological activity before clinical exposure occurs. Human stem cell models, organoid systems and placenta-on-a-chip technology are emerging as promising alternatives to traditional animal testing, allowing researchers to study embryonic development and placental drug transfer with greater precision. Pharmacogenomics and precision medicine are also expected to improve individualized risk prediction by identifying genetic factors that influence fetal susceptibility to teratogenic agents. Furthermore, the integration of electronic health records, pregnancy registries and international pharmacovigilance databases will generate large-

scale real-world evidence, enable earlier detection of rare adverse pregnancy outcomes and supporting safer medication use worldwide. https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-resources

Overall, the history of teratogenicity reflects continuous progress in scientific understanding, regulatory oversight and clinical practice. Lessons learned from historical tragedies have significantly improved maternal and fetal safety, while ongoing technological innovations promise to further enhance the prediction, prevention and management of teratogenic risks in future generations.

What is a Teratogenicity?

Teratogenicity is defined as the ability of an external agent to disturb the normal development of an embryo or fetus, resulting in structural malformations, functional abnormalities, growth restriction, pregnancy loss, or developmental disorders. The agents responsible for these effects are known as teratogens.

Not all fetal abnormalities are caused by medications. Teratogenicity results from a complex interaction between environmental exposures and maternal and fetal genetic factors.

What Is a Teratogen?

A teratogen is any physical, chemical, biological, or environmental factor capable of causing congenital abnormalities during prenatal development.

Examples include:

- Pharmaceutical drugs
- Alcohol
- Tobacco smoke
- Ionizing radiation
- Infectious agents (e.g., rubella virus, cytomegalovirus, Zika virus)
- Heavy metals (lead, mercury)
- Maternal diseases such as uncontrolled diabetes or phenylketonuria

Classification of Teratogens

- Teratogens can be classified into the following categories:

CHEMICAL AGENTS	PHYSICAL AGENTS	BIOLOGICAL AGENTS	MATERNAL CONDITIONS
Pharmaceutical drugs	Ionizing radiation	Rubella virus	Diabetes mellitus
Alcohol	Hyperthermia	Cytomegalovirus	Epilepsy
Industrial chemicals		Toxoplasma gondii	Phenylketonuria
Heavy metals		Zika virus	Nutritional deficiencies

Mechanisms of Drug-Induced Teratogenicity

Mechanisms of Teratogenicity

Teratogenicity refers to the ability of certain medications, chemicals, or environmental factors to interfere with normal embryonic or fetal development when exposure occurs during pregnancy. Such exposure can result in structural malformations, functional impairments, growth restriction, or neurodevelopmental abnormalities in the developing fetus.

The teratogenic potential of a pharmaceutical agent is influenced by several factors, including its chemical characteristics, mechanism of action, dosage, duration of exposure, maternal and fetal genetic susceptibility, and the specific stage of pregnancy during which exposure takes place. Most congenital abnormalities arise from disruptions in key molecular signaling pathways, cellular proliferation, differentiation, migration, or programmed cell death during the critical period of organogenesis (3–8 weeks of gestation). A thorough understanding of these underlying mechanisms is crucial for assessing

teratogenic risk and guiding the safe use of medications during pregnancy. https://pubmed.ncbi.nlm.nih.gov/20061329/

1. Oxidative Stress

Oxidative stress is one of the most common mechanisms underlying drug-induced teratogenicity. It occurs when the production of reactive oxygen species (ROS) exceeds the antioxidant defense capacity of embryonic tissues. Excessive ROS damages cellular lipids, proteins, DNA and mitochondria, impairing normal embryonic development.

The developing embryo possesses relatively immature antioxidant systems, making it particularly susceptible to oxidative injury. Drugs such as phenytoin, valproic acid and certain anticancer agents have been associated with increased oxidative stress and congenital malformations.

2. Interference with Cell Proliferation and Differentiation

Normal embryonic development depends on precise regulation of cell division and differentiation. Certain pharmaceuticals inhibit DNA synthesis, mitosis, or protein synthesis, preventing normal tissue formation.

For example, methotrexate, a folate antagonist, inhibits dihydrofolate reductase, reducing DNA synthesis and rapidly dividing embryonic cells. This interference can lead to severe congenital abnormalities and fetal loss.

3. Apoptosis (Programmed Cell Death)

Apoptosis is a genetically regulated process that removes unnecessary or damaged cells during embryogenesis. Teratogenic drugs may trigger excessive apoptosis, resulting in loss of cells required for normal organ development.
Examples include:

- Retinoids
- Alcohol
- Certain anticonvulsants

Excessive apoptosis during organogenesis may produce severe congenital malformations.

4. Folate Antagonism

Folic acid plays an essential role in DNA synthesis, nucleotide production and methylation reactions during fetal development. Drugs that interfere with folate metabolism reduce cellular proliferation and impair neural tube closure.
Examples include:

- Methotrexate
- Trimethoprim
- Some antiepileptic drugs

Folate deficiency during early pregnancy significantly increases the risk of neural tube defects.

5. Disruption of Molecular Signaling Pathways

Embryonic development is controlled by signaling pathways such as:

- Sonic Hedgehog (SHH)
- Transforming Growth Factor-β (TGF-β)
- Fibroblast Growth Factor (FGF)
- Notch signaling

Certain pharmaceuticals interfere with these pathways, leading to abnormal tissue patterning and organ formation.

Retinoic acid derivatives (such as isotretinoin) are well-known examples that alter gene expression and embryonic patterning.

6. Epigenetic Alterations

Epigenetics refers to heritable changes in gene expression without alterations in the DNA sequence. Pharmaceutical agents may modify:

- DNA methylation
- Histone modification
- MicroRNA expression

These changes may alter fetal development and contribute to congenital abnormalities or diseases that become evident later in life.

Recent research suggests epigenetic mechanisms play an increasingly important role in developmental toxicity.

7. Endocrine Disruption

Some drugs alter maternal or fetal hormone balance, affecting normal organ development and sexual differentiation.
Examples include:

- Androgens
- Anti-androgens
- Certain hormonal therapies

Hormonal imbalance during pregnancy may impair reproductive organ development and endocrine function.

8. Placental Dysfunction

Some medications impair placental blood flow or damage placental tissue, reducing oxygen and nutrient delivery to the fetus.
Consequences include:

- Intrauterine growth restriction (IUGR)
- Low birth weight
- Preterm birth
- Fetal hypoxia

Examples include vasoconstrictive drugs and some chemotherapeutic agents.

9. Genetic Susceptibility

Not all fetuses exposed to a teratogenic drug develop congenital abnormalities. Genetic variations in maternal and fetal enzymes responsible for drug metabolism can influence teratogenic risk.

Examples include polymorphisms in:

- CYP450 enzymes
- Folate metabolism genes
- Drug transporter genes

This explains why similar drug exposures may produce different outcomes among pregnancies.

Mechanisms of Teratogenicity:

Mechanism	Description	Example Drugs
Oxidative stress	Cellular damage by reactive oxygen species	Valproic acid, Phenytoin
Folate antagonism	Inhibits DNA synthesis	Methotrexate, Trimethoprim
Excessive apoptosis	Organ malformations	Isotretinoin
Retinoic acid signaling disruption	Alters embryonic gene expression	Isotretinoin

Angiogenesis inhibition	Reduces blood vessel formation	Thalidomide
DNA synthesis inhibition	Prevents cell proliferation	Methotrexate
Renin-angiotensin inhibition	Impairs fetal kidney development	ACE inhibitors, ARBs
Placental dysfunction	Fetal growth restriction	Vasoconstrictive agents
Prostaglandin inhibition	Premature ductus arteriosus closure	NSAIDs

Critical Periods of Fetal Development and Timing of Drug Exposure

The effect of a teratogenic drug depends not only on the drug itself but also on when exposure occurs during pregnancy. Human embryonic and fetal development is a continuous process in which different organs develop at different times. Consequently, exposure to the same medication may produce completely different outcomes depending on the gestational age. Some drugs may cause miscarriage during early pregnancy, major structural malformations during organ formation, or functional and growth abnormalities later in pregnancy. Understanding these critical developmental periods is essential for safe prescribing and appropriate counseling of pregnant women.

Embryonic development begins at fertilization and continues through a series of highly coordinated processes including cell division, implantation, organogenesis and fetal maturation. During these stages, rapidly dividing cells are particularly sensitive to environmental influences, including medications. Therefore, healthcare professionals must consider both the pharmacological properties of a drug and the stage of fetal development before initiating therapy during pregnancy.

Developmental stage	Gestational Age	Main Characteristics	Potential drug effects
Pre-embryonic	0-2 weeks	Fertilization and implantation	Embryonic death or normal development (all-or-none)
Embryonic	3-8 weeks	Organogenesis	Major structural congenital malformations
Fetal	9 weeks to birth	Growth and organ maturation	Functional abnormalities, growth restrictions, fetotoxicity

Organogenesis: The Most Sensitive Period

Organogenesis occurs approximately between weeks 3 and 8 after fertilization.

- During this period:
- The neural tube closes.
- The heart begins beating.
- Limb buds appear.
- Eyes and ears develop.
- Facial structures form.
- Internal organs differentiate.

Because these organs are developing simultaneously, exposure to teratogenic drugs during organogenesis has the greatest potential to produce irreversible structural abnormalities.

Critical Periods of Major Organ Development

- Organ System
- Most Sensitive Period
- Central nervous system

Weeks 3–16 (functional development continues throughout pregnancy)

WEEKS	3-6	4-5	4-8	4-9	6-8	6-9	7-12
ORGAN DEVELOPMENT	Heart	Upper limbsLower limbs	Eyes	Ears	Teeth	Palate	External genitalia

Exposure during these periods increases the risk of abnormalities affecting the corresponding organ system.

Factors Influencing Fetal Susceptibility

Several factors determine whether drug exposure results in fetal harm:

- Gestational age at exposure
- Drug dosage
- Duration of treatment
- Frequency of exposure
- Placental drug transfer
- Maternal metabolism
- Maternal diseases
- Genetic susceptibility of the mother and fetus
- Concurrent exposure to alcohol, tobacco, or other drugs

These factors explain why similar drug exposures may produce different outcomes among pregnancies.

Clinical Importance

Knowledge of critical developmental periods enables healthcare professionals to:

- Avoid high-risk medications during organogenesis.
- Select safer therapeutic alternatives.
- Counsel women before conception.
- Monitor pregnancies with known drug exposure.
- Reduce preventable congenital anomalies.

Appropriate timing of medication use is an essential component of evidence-based maternal healthcare.

Classification of Teratogenic Pharmaceuticals during pregnancy

Teratogenic medications can be grouped according to their therapeutic use.

Drug class	Examples	Primary Indication	Possible fetal effects
Antiepileptic Drugs (AEDs)	Valproic acid Phenytoin Carbamazepine Phenobarbital	Epilepsy	Neural tube defects Congenital heart defects Craniofacial abnormalities Neurodevelopmental disorders
Retinoids	Isotretinoin Acitretin	Severe acne	Craniofacial abnormalities Cardiac defects Central nervous system malformations Thymic abnormalities
Anticancer and Immunosuppressive Drugs	Methotrexate Mycophenolate mofetil Cyclophosphamide		Miscarriage Growth restriction Skeletal abnormalities Craniofacial defects
Anticoagulants	Warfarin		Fetal warfarin syndrome Nasal hypoplasia Stippled epiphyses

			Central nervous system abnormalities
Antihypertensive Drugs	Enalapril Lisinopril Losartan		Oligohydramnios Renal dysgenesis Pulmonary hypoplasia Neonatal renal failure
Immunomodulatory Drugs	Thalidomide		Limb reduction defects Ear abnormalities Cardiac malformations Cranial nerve defects

Placental Drug Transfer

Placental Drug Transfer

The **placenta** is a specialized transient organ that functions as the primary interface between the maternal and fetal circulatory systems throughout pregnancy. It plays a vital role in supporting fetal development by facilitating the exchange of oxygen, nutrients, hormones, antibodies, waste products, and other endogenous substances between the mother and fetus. Although the placenta offers a degree of protection against potentially harmful compounds, it does not act as a complete barrier. Numerous pharmaceutical agents are capable of crossing the placental membrane and entering the fetal circulation, where they may produce beneficial therapeutic effects or contribute to developmental toxicity, including teratogenic effects.

Consequently, a thorough understanding of placental drug transfer is essential for assessing the safety and potential risks of medication use during pregnancy.

Mechanisms of Drug Transfer Across the Placenta

Pharmaceuticals cross the placenta through several mechanisms depending on their physicochemical properties and the presence of placental transport proteins.

1. Passive Diffusion

Passive diffusion is the most common mechanism of placental drug transfer. It does not require energy and occurs along a concentration gradient from maternal blood to fetal blood.

Drugs that readily cross by passive diffusion generally have:

- Molecular weight less than 500 Da
- High lipid solubility
- Low degree of ionization
- Low plasma protein binding

Examples include ethanol, diazepam and many anesthetic agents.

2. Facilitated Diffusion

Facilitated diffusion uses specific carrier proteins to transport substances across the placental membrane without requiring metabolic energy. This mechanism mainly transports glucose and selected nutrients but can also contribute to the movement of certain drugs.

3. Active Transport

Active transport requires cellular energy (ATP) and specialized transporter proteins. These transporters regulate fetal exposure by either transporting drugs toward the fetus or pumping potentially harmful compounds back into the maternal circulation.

Important placental transporters include:

- P-glycoprotein (ABCB1)
- Breast Cancer Resistance Protein (BCRP/ABCG2)

- Multidrug Resistance-associated Proteins (MRPs)

These proteins act as protective mechanisms by reducing fetal exposure to many medications.

4. Endocytosis and Pinocytosis

Large molecules that cannot diffuse across the placenta may enter through endocytosis or pinocytosis. Maternal immunoglobulin G (IgG) antibodies are transferred by receptor-mediated endocytosis, providing passive immunity to the fetus. This pathway contributes minimally to the transfer of most pharmaceutical agents.

Factors Affecting Placental Drug Transfer

Several factors influence the amount of drug reaching the fetus.

S.no	Drug-related Factors	Maternal Factors	Placental Factors	Fetal Factors
1	Molecular weight	Maternal blood flow	Placental surface area	Fetal blood pH
2	Lipid solubility	Liver metabolism	Placental thickness	Fetal metabolism
3	Degree of ionization	Kidney function	Expression of transport proteins	Fetal metabolism
4	Plasma protein binding	Concurrent medications	Gestational age	Developmental stage of organs
5	Half life	Metarnal disease (Diabetes, hypertension)	Placental blood flow	

Placental Transfer of Drugs

Drug	Crosses Placenta (Yes/No)	Clinical Significance
Valproic acid	Yes	High fetal exposure
Isotretinoin	Yes	Sever embryopathy
Methotrexate	Yes	Fetal toxicity
Warfarin	Yes	Fetal warfarin syndrome
Heparin	No (minimal transfer)	Preferred anti-coagulant during pregnancy
NSAIDs	Yes	Fetal renal toxicity

Pharmacovigilance and Drug Safety Monitoring During Pregnancy

Pharmacovigilance is the science and activities concerned with the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problems. During pregnancy, pharmacovigilance plays a critical role because pregnant women are often excluded from clinical trials, resulting in limited pre-marketing safety data for many medications. Consequently, post-marketing surveillance is essential for identifying potential teratogenic effects, evaluating fetal risks and ensuring the safe use of medicines during pregnancy**.**

Objectives of Pharmacovigilance in Pregnancy

The major objectives are to:

- Detect previously unknown teratogenic effects.
- Monitor the safety of medicines used during pregnancy.
- Evaluate maternal and fetal outcomes following drug exposure.
- Identify risk factors associated with congenital anomalies.
- Support evidence-based prescribing.
- Improve maternal and neonatal safety.

Pregnancy Risk Assessment in Pharmacovigilance

Risk assessment considers several factors:

- Gestational age at exposure
- Drug dosage
- Duration of treatment
- Route of administration
- Maternal diseases
- Genetic susceptibility
- Concurrent medication use

Healthcare professionals should always weigh the benefits of maternal treatment against the potential fetal risks.

Future Perspectives and Emerging Research in Teratogenicity

Despite major advances in developmental toxicology, predicting the teratogenic potential of pharmaceuticals remains challenging. Ethical limitations on clinical research in pregnant women, species differences in animal models and incomplete knowledge of fetal development continue to limit accurate risk assessment. Emerging technologies such as artificial intelligence (AI), pharmacogenomics, organoids, organ-on-a-chip systems and precision medicine are transforming the evaluation of drug safety during pregnancy. These innovations are expected to improve the prediction of teratogenic risk while reducing reliance on animal testing.

1. Artificial Intelligence (AI) in Teratogenicity Prediction

Artificial intelligence and machine learning are increasingly being used to:

- Predict teratogenic potential of new drug candidates.
- Analyze large pharmacovigilance databases.
- Detect early safety signals.
- Support individualized risk prediction.
- Improve clinical decision-making.

AI can integrate data from clinical studies, electronic health records, pregnancy registries, genomics and pharmacovigilance databases to identify patterns that may not be recognized using conventional statistical methods.

2. Pharmacogenomics and Precision Medicine

Genetic variations influence how medications are metabolized by both the mother and the fetus. Pharmacogenomic research aims to identify genetic factors associated with:

- Drug metabolism
- Placental drug transport
- Susceptibility to congenital anomalies
- Individual differences in teratogenic risk

Future precision medicine approaches may allow clinicians to select the safest medication based on each patient's genetic profile.

3. Human Organoid Technology

Human organoids are three-dimensional miniature tissues derived from stem cells that closely mimic human organs.
Examples include:

- Brain organoids
- Cardiac organoids
- Liver organoids

- Kidney organoids
- Placental organoids

These models provide more physiologically relevant systems for studying developmental toxicity than conventional cell cultures and can improve prediction of human-specific teratogenic effects.

4. Organ-on-a-Chip Technology

Organ-on-a-chip systems combine living human cells with microfluidic devices to simulate organ function. Potential applications include:

- Placenta on a chip model
- Maternal fetal drug transfer studies
- Drug toxicity testing
- Pharmacokinetic studies

These platforms may reduce dependence on animal models while improving prediction of fetal drug exposure.

5. Stem Cell Research

Human induced pluripotent stem cells (iPSCs) have become valuable tools for studying embryonic development.
Applications include:

- Developmental toxicity screening
- Disease modeling
- Drug safety evaluation
- Personalized medicine

Stem cell technologies enable researchers to investigate early developmental events that cannot be ethically studied in pregnant women.

6. Improved Pregnancy Registries

Future pregnancy registries are expected to:

- Include larger international populations.
- Collect long-term developmental outcomes.
- Integrate genomic and pharmacogenomic data.
- Improve detection of rare congenital anomalies.
- Support global collaboration in medication safety.

These registries will strengthen evidence regarding medication use during pregnancy.

7. Advanced Pharmacovigilance

Future pharmacovigilance systems will increasingly utilize:

- Artificial intelligence
- Big data analytics
- Real-world evidence
- Electronic health records
- Mobile health applications

These approaches may enable earlier identification of medication-related fetal risks and improve patient safety.

8. Regulatory Developments

Regulatory agencies continue to improve pregnancy safety evaluation through:

- Enhanced pregnancy exposure registries.

- Better drug labeling.
- International collaboration.
- Improved post-marketing surveillance.
- Standardized developmental toxicity testing.

Future regulatory policies are expected to increase transparency regarding medication safety during pregnancy.

9. Challenges for Future Research

Important challenges remain, including:

- Limited clinical trials involving pregnant women.
- Ethical constraints.
- Rare exposure to certain medications.
- Long-term follow-up of exposed children.
- Limited data from low- and middle-income countries.
- Standardization of emerging laboratory models.

Addressing these challenges will improve the quality of evidence for medication safety.

Conclusion

Teratogenicity continues to be an important topic in maternal and fetal medicine due to its potential to cause serious congenital abnormalities and adverse pregnancy outcomes. This review highlights that the teratogenic potential of a drug depends on several factors, including the stage of pregnancy, dosage, duration of exposure, maternal health and genetic susceptibility. While many medications are necessary for managing maternal diseases their use during pregnancy should be based on a careful assessment of both maternal benefits and fetal risks.

This review also highlights the increasing importance of **pharmacovigilance**, pregnancy exposure registries, and evolving regulatory guidelines in enhancing the safe use of medications during pregnancy. Furthermore, recent advancements in pharmacogenomics, artificial intelligence, and developmental toxicology provide promising approaches for improving the prediction, identification, and prevention of teratogenic risks. Ongoing research, evidence-based prescribing practices, and comprehensive patient counseling remain essential for reducing fetal risk while ensuring optimal maternal care. Collectively, these strategies support a balanced, evidence-based approach to medication use during pregnancy, ultimately contributing to improved maternal and fetal health outcomes.

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