

A Review on Teratology

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Abstract: In this review, we provide an overview of the basic principles of teratology, beginning with its definition, the critical point for teratogenesis to occur and the most evident etiological agents to improve the understanding of the science. Teratology is a recent science that began in the early twentieth century, and has greatly improved over the recent years with the advancements in molecular biology, toxicology, animal laboratory science, and genetics, as well as the improvement on the knowledge of the environmental influences. Nevertheless, more work is required to reduce the influence of hazardous products that could be deleterious during pregnancy, thus reducing teratogenic defects in the newborn. While some teratogenic defects are attributed to their agents with certainty, the same for a lot of other such defects is lacking, necessitating consistent studies to decipher the influence of various teratogenic agents on their corresponding teratogenic defects.

Keywords: Basic principles; Environmental agents; Etiological agents; Genetic factors; Maternal conditions; Teratology

INTRODUCTION

Medication treatment during pregnancy is a particular source of concern due to the risk of teratogenic consequences and physiologic changes in the mother as a result of the pregnancy [1]. The pharmacokinetics of drugs taken are affected by pregnant physiology, and some medications can reach the fetus and harm it [2]. Historical events such as the thalidomide crisis in the 1960s and the discovery of teratogenic effects associated with the use of diethylstilboestrol in 1971 have influenced public perceptions of medication use during pregnancy and lactation [3]. Following these incidents, the US Food and Drug Administration enacted severe restrictions governing drug labeling and the use of pharmaceuticals during pregnancy, demanding demonstrations of a drug's safety and efficacy before it can be sold [4].

Teratogenesis is the process of the fetus developing abnormalities. Such a defect is caused by a teratogen. The term "teratogen" is commonly used to describe a substance that causes anatomical abnormalities in a developing embryo. Radiation, chemicals (drugs), and pathogenic agents are examples of teratogens.

Many birth abnormalities have unclear causal routes, making them the greatest cause of infant mortality. A specific birth defect can be caused by a variety of factors and mechanisms (e.g., genetics, environmental agents, medications, physical conditions), whereas a specific pathogenic process can result in different outcomes for chemical or drug exposures depending on factors like embryonic age, duration and dose of exposure, and genetic susceptibility. We will offer an overview of the most major teratogenic pathways known today, even though the methods by which medications may cause birth abnormalities are still unknown. Identifying these pathways could be beneficial for drug development, post-marketing research, and the prescription of medicine to women during their reproductive years [5].

• WHAT IS TERATOLOGY?

Teratology is the study of aberrant embryonic development and the causes of birth abnormalities and congenital deformities. These structural or anatomical anomalies are present at birth but may not be diagnosed until later in life. They can be visible on the body's surface or within the viscera. Around 20% of perinatal deaths are caused by congenital abnormalities. Approximately 3% of newborn babies will be born with serious abnormalities, with another 3% having defects discovered later in life.

Teratology is the field that investigates birth defects, congenital deformities, and developmental disorders (CDDs). Teratology is derived from the Greek word teratos, which means "monster." Because of the combined effects of internal and external stimuli during the prenatal developmental phase, these abnormalities may be visible or latent at birth.

• HISTORY OF TERATOLOGY

Several teratological studies have concluded that environmental-induced deformities first emerged as a modern science in the 1930s, with the publication of a series of experiments in which pregnant pigs were fed a vitamin A-deficient diet. The defects in the progeny revealed that mammalian development was not as well safeguarded as previously thought due to its residency within the mother. These experiments revealed that even minor changes in the environment can have catastrophic consequences for the embryo. In a series of studies in experimental animals using congeners of biologically important molecules like the amino acid mimic azaserine, the susceptibility of mammalian embryos to toxicity from xenobiotic agents was demonstrated [6].

The early 1960s thalidomide incident advanced our understanding of developmental toxicology by demonstrating an agent with low adult toxicity but substantial embryo toxicity. Many investigations examining the harmful potential of medicines taken during pregnancy still rely on selective embryotoxicity. Regulatory authorities, particularly the Food and Drug Administration in the United States, set procedures for testing pharmaceuticals in animals prior to marketing clearance in the 1960s. To increase confidence that a biologically relevant dose for that species was included in the test procedure, drug trials were required to employ levels high enough to produce maternal toxicity [7].

The recognition that maternal disposition (metabolism and distribution) of the drug affects the medication's effect on the foetus is part of the solution to the difficulty of extrapolating results from animals to humans. When rats are administered thalidomide orally, it is poorly absorbed. As a result, in conventional oral teratology experiments, administration of the medication does not result in a meaningful dose reaching the embryo. When thalidomide is rendered soluble in dimethyl sulfoxide and administered parenterally, its ability to harm the foetus approaches that of rabbits, a species that is extremely vulnerable to thalidomide effects [8].

• PRINCIPLES OF TERATOLOGY [9]

It's vital to remember that almost all teratogen-induced birth abnormalities can be avoided if we understand the six basic teratology principles.

Principle 1: *Teratogenesis susceptibility is determined by the conceptus' genotype and how it interacts with the environment.*

When reviewing what is known about the impacts of recognised human teratogens, two of the most distinguishing characteristics of teratogens are that they cause a varied phenotypic in exposed and afflicted children, and that not all exposed infants are affected (i.e., susceptibility is variable).

Variable phenotype: In teratogen-affected newborns, the range of phenotypic expression is extraordinarily broad. Over the last three decades, enough evidence has developed in the clinical literature to demonstrate that most teratogens generate a consistent pattern of abnormalities that varies between people.

Variable susceptibility: Only a tiny percentage of infants that are exposed to known or suspected teratogens in utero experience any negative effects. Although it is unclear why some fetuses are more vulnerable, it is widely assumed that susceptibility is caused by inheriting a collection of genes that interact with the teratogenic agent, disrupting normal morphogenetic pathways and resulting in the birth abnormality. Because despite a wide variety of in utero exposures, only a small percentage of newborns appear with birth abnormalities, it might be difficult for physicians and families to trust that particular substances have teratogenic potential.

Susceptibility to phenytoin: Clinical experience with phenytoin, an anticonvulsant medication, shows how varied phenotypes and susceptibilities interact. Craniofacial dysmorphism, growth deficits, limb deformities, and developmental delay are among the malformations associated with maternal phenytoin exposure. A short nose with anteverted nostrils, a long philtrum, and a distinctively bent upper lip is all facial traits associated with phenytoin exposure. The inner canthal skinfolds are unnecessary because the nasal bridge is large and low.

Principle 2: *The developmental stage at which a teratogenic substance is exposed affects susceptibility.*

The fact that developing organisms are more susceptible to change than mature, fully evolved species is a basic biological fact. This means that increased vulnerability persists throughout the embryo's development, though not always at the same rate.

It is necessary to explore human embryology quickly to apply this idea to human development. There is a period after fertilization but before implantation when the zygote splits but does not become larger (the pre-implantation period). Because all of the embryo's cells are totipotent (meaning they can develop into any tissue) at this point, the death of a few cells will not cause any defects. The embryo implants as a blastocyst in the uterus, with two layers of inner cell mass. Some cells will help to grow the embryo itself, while others will help to develop the extraembryonic membranes. Neurulation, which occurs between weeks 3 and 5, is a significant developmental milestone. Organogenesis occurs between weeks 3 and 8, and is marked by the segregation of cell groups into primordia that will eventually form the future organs. Histogenesis starts before organogenesis is finished and lasts till after parturition.

Principle 3: *Teratogenic substances cause aberrant embryogenesis by acting on developing cells and tissues in specific ways (mechanisms) (pathogenesis)*

The term "mechanism" refers to the first, and often only, occurrence in a chain of events that connects cause and effect. The first event is arguably the most crucial of the sequence, not only because it serves as a link between the cause and the subsequent physiologic changes, but also because it has the potential to impact the nature of these latter changes.

Teratogenic exposures cause modifications that aren't always specific to the causal variables. Ionizing radiation can cause mutations, chromosomal abnormalities, mitotic interference, and enzyme inhibition, among other things.

Principle 4: *Death, deformity, growth retardation, and functional disorder are the final signs of aberrant development.*

The repercussions of aberrant development are not equally likely and are most likely linked to the time of exposure about fetal development. Although anyone, or even all, of these outcomes, may occur if enough embryotoxic agents were injected at high sensitivity times, certain manifestations are more likely to occur at specific stages.

Principle 5: *The ability of a harmful environmental agent to reach growing tissues is determined by the agent's nature (influences)*

The maternal dose, route of admission, physical qualities (solid, liquid, or gas), and rate of absorption into the systemic circulation are all important aspects to consider when evaluating whether a chemical will reach the foetus. Detoxification enzymes for xenobiotic compounds are present in the maternal system, reducing the amount of the "parent chemical" that reaches the foetus (although the metabolites themselves may have teratogenic properties).

Principle 6: *As the dosage is increased from having no impact to fatal, the indications of aberrant development become more severe*

Teratogens and teratogenic activity have a dose-response connection, just like medications and therapeutic effect. This idea must be considered while determining thresholds for various toxicologic consequences.

The no-effect or threshold level for adverse effects is regarded an important benchmark for regulators aiming to determine medicine or product safety. Is there a dose that doesn't have any negative side effects? Is this dose therapeutically effective, if so? If a given dose causes negative consequences, increasing or decreasing the dose should increase or decrease the occurrence and danger of negative consequences.

When a reasonable range of dosages was used in conventional teratogenicity studies, no-effect levels were frequently observed when mortality and deformities were the endpoints for adverse effects. Growth retardation is likely to be the same way. However, there is doubt about functional abnormalities produced by teratogen exposures due to a dearth of information in the literature. All

signs of aberrant development begin to show only when the dosage exceeds a proven threshold, according to teratogen experience. In contrast, there is a smaller dosage range where no embryotoxic effects occur.

• **MECHANISM OF ACTION OF TERATOGENESIS** [10]

The most common mechanisms of action of teratogens are hyperacetylation, cholesterol imbalance, alteration of folate metabolism and folate antagonism, retinoic acid imbalance, endocrine disruption, vascular disruption and oxidative stress.

➤ **Hyperacetylation:**

Hyperacetylation can occur when the histone deacetylase enzyme (HDAC) is inhibited, and the acetylation status of histones influences chromatin structure and gene expression, interfering with embryonic development. Once carcinogenesis is prevented, HDAC inhibitors are employed as anticonvulsants (valproic acid) and cancer treatments. TSA, apicidin, and sodium butyrate are examples of anticancer medicines. Hyperacetylation is induced by these medications in animal embryos, resulting in congenital abnormalities such as neural tube and axial skeletal deformities.

➤ **Cholesterol imbalance:**

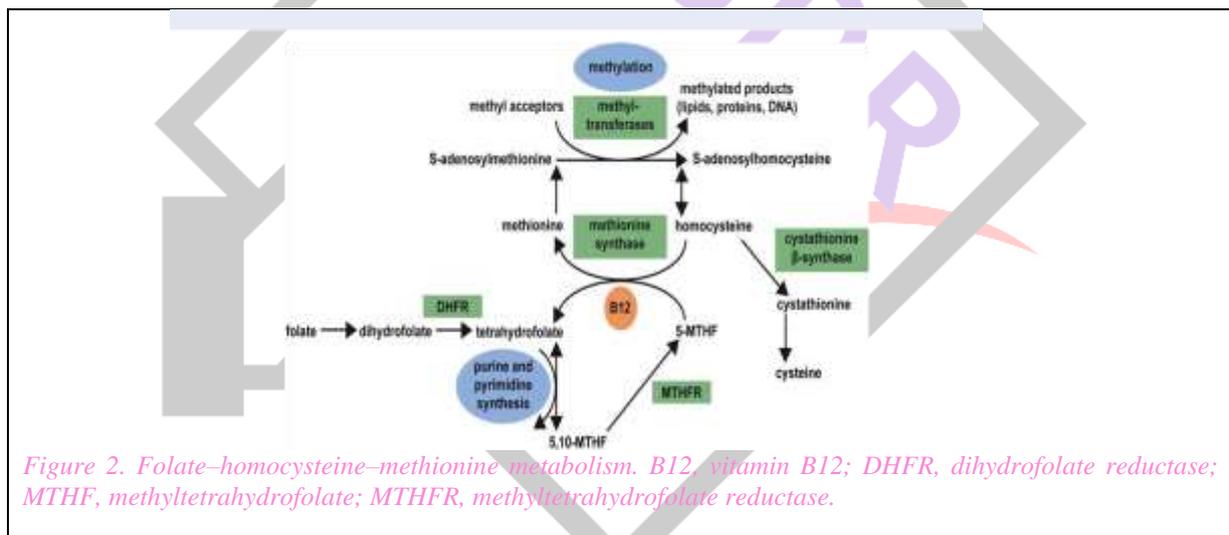
Foetal development necessitates a large amount of cholesterol. During early pregnancy, the mother provides this biomolecule and transports it to the foetus via the placenta, whereas late pregnancy relies on the foetus' creation. Statins, for example, block HMG CoA reductase, an enzyme involved in cholesterol production. HMG-CoA reductase converts to mevalonate, which disrupts cholesterol synthesis and can harm a developing foetus.

➤ **Alteration in folate metabolism and folate antagonism:**

Folate, also known as water-soluble vitamin B, is a co-enzyme that works as a receiver or donor of one-carbon unit in biochemical reactions and is involved in purine and pyrimidine production as well as DNA methylation. During embryogenesis, increased cell development and tissue proliferation require an increase in DNA synthesis, which requires the availability of folate. Some medicines inhibit the conversion of folate to tetrahydrofolate by competing with dihydrofolate reductase. Neural tube defects, orofacial clefts, and limb defects are the most common birth defects associated with these drugs.

➤ **Retinoic acid imbalance:**

Once this Vitamin A precursor is strongly associated to vertebrate morphogenesis, an imbalance between synthesis and degradation of retinoic acid can occur in an excess or deficit of this acid, resulting in negative consequences on cells and embryos. Isotretinoin, for example, can cause a retinoic acid imbalance, which can lead to craniofacial and axial skeleton abnormalities.



➤ **Endocrine disruptors:**

Endocrine disruptors have the potential to impair hormone release and hormone receptor-mediated reactions. Endocrine disruptors include bisphenol A and phthalates, as well as diethylstilbesterol, oral contraceptives, fertility therapy medicines, and other endocrine disrupting substances.

➤ **Disruption of the vessels:**

Blood perfusion in embryonic tissues will be disrupted due to changes in vein, artery, and capillary development. Anatomical problems, maternal chronic diseases, or exposure to teratogenic agents during pregnancy, such as misoprostol, phenytoin, cocaine, ergotamine, and some vasodilator and vasoconstrictor drugs, can cause these maternal-foetal blood disturbances, which can include hyperperfusion, hypoperfusion, hypoxia, and obstruction. The most frequent birth malformations, particularly limb deformities, are structural

➤ **Oxidative stress:**

The reactive oxygen species (ROS), which provide oxidation-reduction reactions, cause oxidative damage to cellular macromolecules such as lipids, proteins, DNA, and RNA. UV, UVA, and UVB radiation, ionizing radiation, and chemical agents are examples of exogenous ROS sources, whereas endogenous sources are linked to cellular metabolism or oxidase enzymes. Embryonic cytochrome P450 enzymes can bioactivate certain of these substances (sometimes referred to as proteratogens). The intracellular balance between proteratogen bioactivation, molecular target damage, maternal proteratogen clearance, and injured

cell repair will determine if they are teratogenic. Thalidomide, valproic acid, phenytoin, alcohol, and anticancer medications are some of the pharmaceuticals that cause oxidative stress.

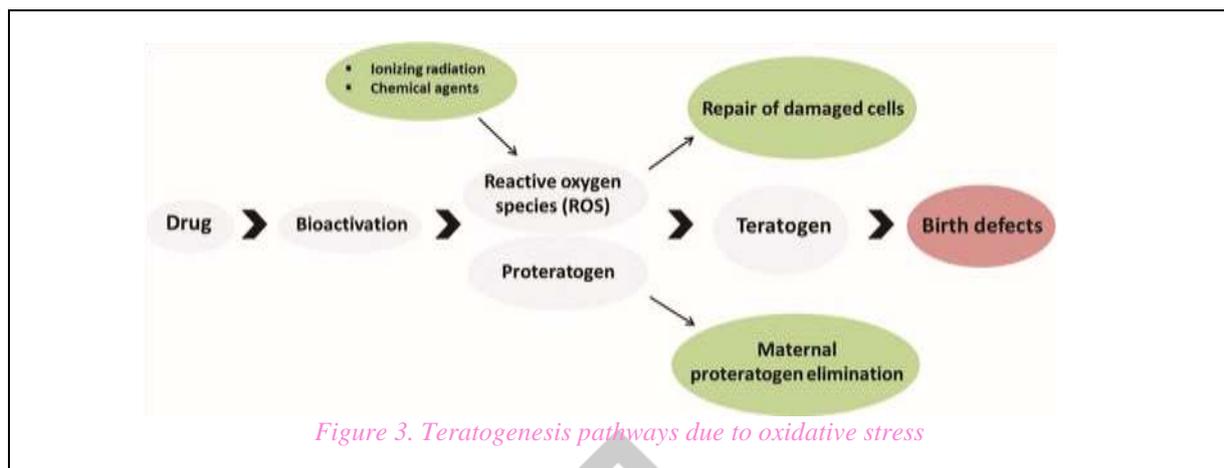


Figure 3. Teratogenesis pathways due to oxidative stress

- **PHYSIOLOGICAL CHANGES IN PREGNANCY**

Weight increase and a change in body shape are the most noticeable physical changes. Breast tissue, blood, and water volume in the form of additional vascular and extracellular fluid cause weight growth. Maternal reserves are supplemented by fat and protein deposition as well as increased cellular water. During pregnancy, the average weight gain is 12.5 kg. Protein is responsible for 1 kg of weight gain during a normal pregnancy. In addition, plasma albumin levels are lower and fibrinogen levels are higher. During pregnancy, total body fat rises. Plasma lipids rise during the second half of pregnancy, while triglycerides, cholesterol, and lipoproteins fall immediately after birth. During pregnancy, the ratio of LDL to HDL increases ^[11].

- **PHARMACOKINETICS IN PREGNANCY**

The pharmacokinetics of drugs taken by pregnant women are affected by the physiologic changes of pregnancy. During pregnancy, a woman's plasma volume increases by 30-50 percent, but her cardiac output and glomerular filtration rate increase in proportion. These variables can lead to subtherapeutic medication levels and lower circulating concentrations of some pharmaceuticals (particularly those excreted by the kidney). Additionally, during pregnancy, body fat levels rise, increasing the volume of fat-soluble medication distribution. The volume of distribution for highly protein-bound medicines such as anticonvulsants rises when plasma albumin concentration falls during pregnancy. However, the kidney and liver eliminate unbound medicines more quickly, counteracting the impact of expanded distribution volume ^[12].

Other common medications used during pregnancy, such as antacids, iron, and vitamins, may bind and inactivate some pharmaceuticals. Increased blood flow boosts systemic drug absorption and the rate of commencement of effect, making intramuscular medication absorption faster. Finally, estrogen and progesterone change the activity of hepatic enzymes, which might cause drug build up or impede drug clearance ^[13].

- **PLACENTAL TRANSFER OF DRUGS**

The placenta is a functional unit that connects foetal and mother blood. The placenta maintains foetal and maternal health by performing processes such as nourishment, respiration, metabolism, excretion, and endocrine activity. A medication must diffuse from maternal to foetal circulation through the placenta in order to have a teratogenic or pharmacological effect on the foetus. The drug's chemical properties, such as protein binding, pH difference, lipid solubility, and molecular weight, determine the rate of transfer. The placenta only allows unbound drugs to pass through. During pregnancy, maternal albumin levels drop while foetal albumin rises. As a result, the free drug concentration rises, crossing the placenta and reaching the foetus ^[14].

Low-molecular-weight drugs (less than 500 g/mol) pass freely across the placenta. Medications having a greater molecular weight (between 500 and 1000 g/mol) have a harder time crossing the placenta, and a few drugs with a high molecular weight (>1000 g/mol) do not cross at all. Due to increased maternal and placental blood flow, decreased thickness, and increased surface area of the placenta, medication transplacental transfer rises in the third trimester ^[15].

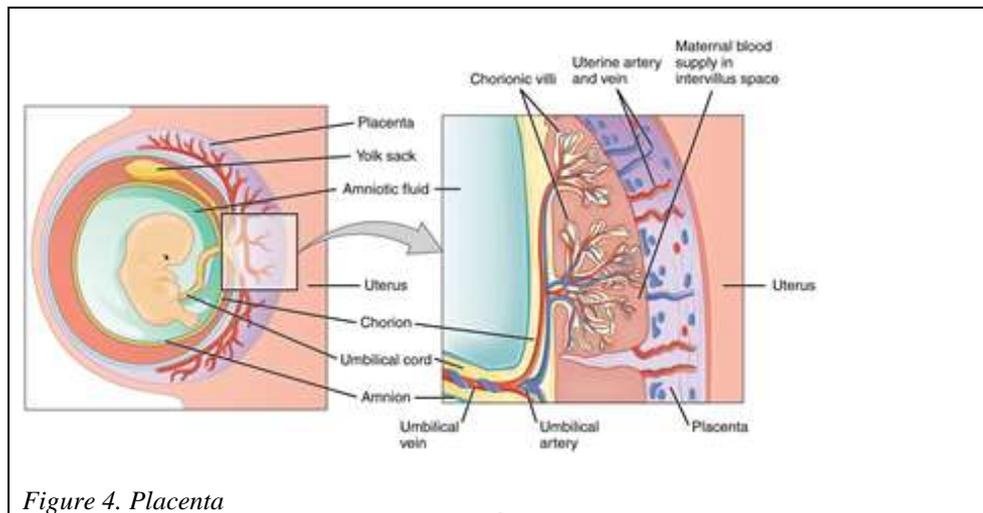


Figure 4. Placenta

Factors controlling placental drug transfer are ^[15]:

1. **Physiochemical Properties of the Drug:**

a. **Lipid solubility and ionization:**

- ✓ *Drugs that are lipid-soluble easily penetrate the placenta and reach the fetal blood. Thiopental, for example, passes the placenta and causes drowsiness and apnea in newborns.*
- ✓ *Ionized medicines cross the placenta slowly, resulting in a fetus with a very low concentration. Succinylcholine and Pancuronium are two examples (of skeletal muscle relaxants).*

b. **Molecular Size:**

- ✓ *The placenta is easily crossed with MW of 250-500.*
- ✓ *The placenta is more difficult to pass with MW of 500-1000.*
- ✓ *The placenta cannot be crossed by MW >1000. Heparin, for example.*

c. **Protein Binding:**

- ✓ *Protein binding in the maternal circulation obstructs medication transport. Propylthiouracil, chloramphenicol, and heparin are three examples.*

2. **Stage of placental and foetal development:**

a. **Blastocyst Formation:**

This occurs between 1 and 16 days in the first trimester and is the time when the zygote divides and the embryo is implanted (pre-differentiation). Drugs have a one-size-fits-all effect. Prenatal death and abortion are caused by medication exposure during this time.

b. **Organogenesis:**

Organogenesis is the process by which an organism develops. During the first trimester, it occurs every 17-60 days. It is the process by which cells differentiate into tissues and organs. It is the most delicate two months of pregnancy. When children are exposed to dangerous medications during this time, they develop significant birth abnormalities or gross malformations (teratogenesis).

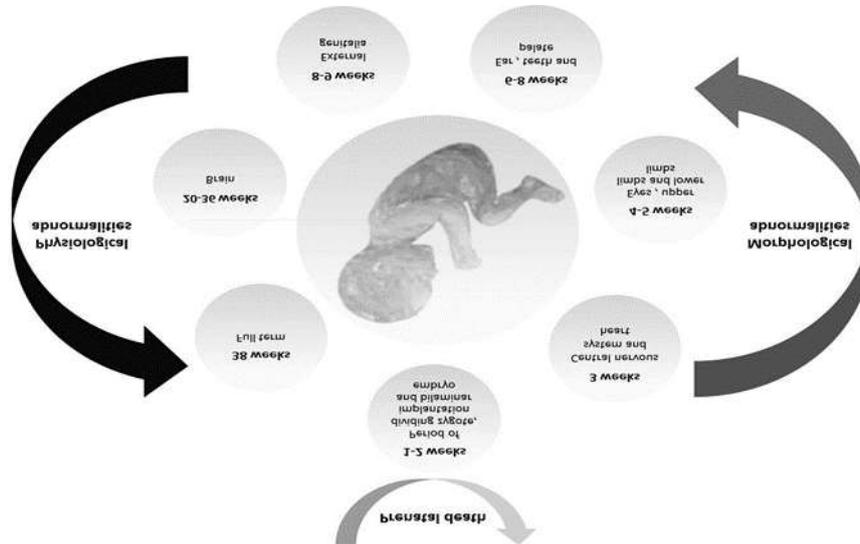
c. Histogenesis and Functional Maturation:

Growth and foetal development (maturation) occur at this stage (2nd and 3rd trimesters). Drug use at this time period resulted in functional issues, minor morphological defects, and growth retardation rather than major malformations. The CNS, on the other hand, is vulnerable to toxic effects throughout pregnancy.

d. Short-term:

Between the 29th and 40th weeks. Drug exposure has an unfavourable effect on labour and neonates after delivery.

Figure 5: Conceptus development stage



• **TERATOGENIC DRUGS**

During the last few decades, it has been clear that medicines given to women during pregnancy may have negative consequences for the foetus' physical development. Thalidomide is a well-known example of how an apparently harmless over-the-counter morning sickness drug can have such a negative impact on the unborn, resulting in miscarriages and physical deformities. FDA has been using the Pregnancy and Lactation Labelling Rule (PLLR) since 2015 to better categorise drug safety, replacing the "A, B, C, D, X" pregnancy labelling categories [16].

➤ **FDA Classification**

Category	Characteristics	Examples
A	<ul style="list-style-type: none"> Adequate and well-controlled human studies have failed to demonstrate a risk to fetus Drugs can be used in pregnancy 	Folic acid Thyroxine
B	<ul style="list-style-type: none"> No risk in animal studies No adequate and well-controlled human studies Drugs can be used in pregnancy 	Paracetamol Erythromycin
C	<ul style="list-style-type: none"> Adverse effects on the fetus in animals only No adequate and well-controlled studies in humans. Risk cannot be ruled out Drug may be used in serious situation despite its potential risk 	Morphine
D	<ul style="list-style-type: none"> Positive evidence of human fetal risk based on adverse reaction data from studies in humans, investigational or marketing experience May be used in serious diseases or life threatening situations Used in cases where benefits outweigh risks 	Antiepileptics
X	<ul style="list-style-type: none"> Proven fetal abnormalities in animal and human studies The risks involved in the use of the drug in pregnant women clearly outweigh potential benefits. Drugs are teratogens and contraindicated in pregnant women or planning to conceive. 	Thalidomide (sedative)

• **DRUGS OF CHOICE**

HYPERTENSION	
Probably Safe	Contraindicated
<ul style="list-style-type: none"> α -methyl dopa Labetalol Emergency ONLY: <ul style="list-style-type: none"> Hydralazine Labetalol 	<ul style="list-style-type: none"> ACE inhibitors Angiotensin II receptor blockers Thiazide diuretics Propranolol Ca²⁺ channel blockers in mild HTN
COAGULATION DISORDERS	
Probably Safe	Contraindicated
<ul style="list-style-type: none"> Heparin 	<ul style="list-style-type: none"> Warfarin
ANTIBIOTICS	

Probably Safe		Contraindicated	
<ul style="list-style-type: none"> • Penicillins (ampicillin, amoxicillin) • Cephalosporins • Macrolides (erythromycin, azithromycin) As an alternative in penicillin-sensitive patients but erythromycin estolate should be avoided (risk of hepatic injury to mother) 		<ul style="list-style-type: none"> • Tetracyclines → teeth and bones deformities • Quinolones (ciprofloxacin) → arthropathy (Bone and cartilage damage) • Aminoglycosides → ototoxicity • Sulfonamides → neonatal jaundice and kernicterus • Chloramphenicol → Gray baby syndrome 	
ANTITHYROID DRUGS			
<ul style="list-style-type: none"> • Are used in thyrotoxicosis or Grave’s disease <ul style="list-style-type: none"> ○ Propylthiouracil ○ Methylthiouracil ○ Carbimazole ○ Radioactive iodine • All can cross the placenta • All have risk for congenital hypothyroidism and goiter • The lowest dose of antithyroid drugs should be used • Propylthiouracil is preferable over others 			
OTHER DRUGS			
Antidiabetics	<ul style="list-style-type: none"> • Insulin is the best choice • Avoid oral antidiabetics 		
Analgesics	<ul style="list-style-type: none"> • Acetaminophen is the best choice 		
Anticonvulsants	All antiepileptics have potential to cause malformations ★ Avoid valproic acid because it’s highly teratogenic • Folic acid supplementations can prevent neural tube defects associated with antiepileptics		

• **HOW NUTRITION INFLUENCE DEVELOPMENT?**

Congenital deformities in animals and humans are caused by vitamin deficiencies. The link between an iodine deficit (necessary for thyroid hormone production), goitre, and cretinism, a neurologic illness marked by severe cognitive impairment, was discovered in the eighteenth century, and it constitutes the first observation of the link between food and birth outcome. Iodine shortage can result in foetal mortality, severe growth restriction, improper bone development, and varied degrees of mental disability if it occurs during pregnancy.

In the 1930s, vitamin A deficiency was discovered to be teratogenic in pigs. Warkany and his colleagues went on to describe the abnormalities that vitamin A deprivation causes in the rodent's almost every organ system. Human malformations caused by vitamin A insufficiency are uncommon, yet vitamin A deficiency remains the greatest cause of visual impairment and blindness in underdeveloped nations.

Low vitamin D levels in the mother are linked to stunted infant growth, neonatal hypocalcemia, and impaired bone mineralization. In animals, zinc deficiency is teratogenic, affecting the development of nearly every organ system. Women with acrodermatitis enteropathy, a hereditary condition affecting zinc absorption, have a greater prevalence of deformities in their offspring.

Copper deficiency during pregnancy has been found to have negative impacts on a variety of species, including humans. Neonatal ataxia and cardiac atrophy are seen in copper-deficient lambs. These babies have cognitive impairment as well as significant cardiovascular and connective tissue abnormalities, which usually result in mortality by the age of three ^[17].

• **DIAGNOSIS OF BIRTH DEFECTS ^[18]**

Screening and diagnostic tests are two types of tests used in clinical care. Screening tests are used to identify people in the general population who are at higher risk than the average to find an interesting disease. Diagnostic tests are used to determine if a person is infected or not. In obstetrics, routine tests are usually performed on all pregnant women to identify people at high risk of having a baby with a birth defect. Then a diagnostic test was performed to determine which of the women had a child with the disease. Many prenatal diagnoses are invasive, have a high risk of complications of pregnancy and miscarriage, and are not always sought by patients or families.

At birth, liveborn newborns have a 2–4% chance of having a birth defect. There is currently no prenatal screening or diagnostic tool that can detect all of this risk. Ultrasound, maternal blood, amniotic fluid, chorionic villi, or foetal blood are all used in prenatal screening and diagnostic testing.

➤ **Ultrasound:**

Ultrasound, commonly known as sonography, creates an image of tissue surfaces by reflecting sound waves. These photos of the embryo and foetus can be extremely detailed, almost photographic in nature. Ultrasound can confirm a healthy pregnancy, determine the gestational age, and detect twins or other multiple pregnancies. Ultrasound can also reveal foetal anomalies, and it's typically the only prenatal test that can be used after a teratogenic exposure, whether it's suspected or confirmed.



Figure 5. Ultrasound image of a normal first trimester embryo in profile. The “+” signs mark the nuchal translucency measurement

Maternal Serum Screening:

At 14-23 weeks of pregnancy, a test of the mother's serum alpha-fetoprotein (MSAFP) can be used to see if the foetus is at risk for an open neural tube defect, the most common of which is spina bifida. Alpha-fetoprotein (AFP) is produced by the foetal liver and excreted in the fetus' urine. However, some AFPs cross the placenta and can be measured in maternal serum. Because mean maternal serum and amniotic AFP concentrations vary with gestational age, results are expressed as a multiple of the mean or MoM.

➤ **Cell free foetal DNA:**

In every pregnancy, the mother's blood contains some placental DNA that is comparable to that of the fetus. The mother's blood contains free DNA that comes from both her cells and the placenta. Excess levels (or shortfalls) of specific chromosomes can be identified via nucleic acid amplification or other molecular approaches, resulting in a new type of aneuploidy test. Cell-free DNA is being used as a screening test for trisomy 13, 18, and 21, as well as aneuploidies of the sex chromosome. Small deletions on other chromosomes, which have a lesser predictive value, are also screened in certain laboratories. The predictive value of cell-free DNA testing is determined by the mother's age.

Diagnostic testing:

Four different procedures can diagnose chromosomal abnormalities:

1. *Preimplantation embryo biopsy:* After in vitro fertilization, the earliest test that may be performed is a biopsy of the early conceptus (IVF). On day 3 or 5, a fertilized egg cleaves into increasingly smaller cells, one or more of which can be taken for examination. This method is occasionally used in couples who are at risk of producing a kid with a major genetic condition like cystic fibrosis. Specific genes from a single embryonic cell can be evaluated using nucleic acid amplification techniques like polymerase chain reaction (PCR) and molecular techniques like chromosomal microarray and gene sequencing to determine if the embryo will be damaged.
2. CVS is done between 10 and 12 weeks following the last menstrual cycle. CVS includes suctioning chorionic villi, or fragments of placental tissue, through a needle or a thin tube. The chromosomal makeup of these fragments of placental tissue is generally identical to that of the embryo. The chromosomal complement of cells from the chorionic villi is examined after they have been developed in culture. CVS is done under ultrasound supervision, and samples can be taken through the cervix or the abdomen, depending on the operator's preference and the placenta's position in the uterus. The chance of miscarriage is typically quoted as 1/400, however with more skilled operators, the risk is significantly reduced.
3. In the second trimester, amniocentesis, or amniotic fluid sample, is done; chromosomal analysis is done on cells that originated in the foetal skin and have the same chromosomes as the remainder of the foetus. The presence of AFP in amniotic fluid is used to check for an open neural tube and a few other abnormalities. Patients are told that amniocentesis conducted under continuous ultrasound supervision has a 1/500 risk of miscarriage, albeit this risk is decreased with skilled operators.
4. After 18 weeks of pregnancy, foetal blood sampling includes collecting a blood sample straight from the foetus. This treatment includes drawing blood from the umbilical vein, preferably around the placental implantation site, and is linked to a 1–3% risk of foetal loss. If a risk has been identified based on family history, parent testing, or the results of other tests, a sample of foetal blood for chromosome or genetic analysis may provide a faster answer to specific questions, but other test methods are generally preferred due to less demanding technical requirements.

- **PREVENTION OF BIRTH DEFECTS**

Primary prevention of birth abnormalities saves both the afflicted children and their parents a lot of money and time. Primary prevention includes screening for and treating illnesses in women before conception, quitting smoking and abusing alcohol or "recreational drugs," maintaining a healthy body weight, getting enough exercise, and eating a healthy diet rich in folic acid and essential vitamins, among other things.

Understanding the possible causes of congenital abnormalities can lead to more appropriate care and counseling, as well as the reduction of fear or guilt, and provide families the chance to make better reproductive options in the future. The discovery of a teratogenic cause alerts the lady and her healthcare practitioner, and it opens the door to birth control ^[19].

- **CONCLUSION**

The particular nature of pregnancy physiology poses obstacles to pharmacological treatment of chronic and acute diseases, as well as symptom management of numerous pregnancy-related ailments. All physicians, including pharmacists, have a duty to provide patients with thorough, accurate, and up-to-date information about the risks and benefits of taking drugs during pregnancy. To properly counsel women who have been exposed to pharmaceuticals about the danger of teratogens, it is necessary to precisely identify exposure and measure the quantity of exposure. This may be simple with prescription pharmaceuticals, but it can be considerably more difficult with ethanol, other illegal narcotics, or over-the-counter medications. Also, while newer options may be available, medications that have been in use for a long time are frequently preferred when choosing pharmaceuticals to take during pregnancy. This is because foetal safety has been demonstrated. Patients should be informed about non-drug options for dealing with stress, aches and pains, and virus infections during pregnancy. Any medicine should be taken only if the risk-to-benefit ratio justifies it, and the lowest effective dose should be employed. Patients should be informed about the dangers of social drug use. Because the long-term consequences of medications in the uterus may not be known for many years, any drug usage during pregnancy should be approached with caution.

- **SUMMARY**

A teratogen is any plant, food, nutritional status, or physical factor that can interfere with normal foetal development and cause a congenital deformity to occur. Teratogenesis is defined as the elimination of a threshold number of cells that the foetus is unable to replace by subsequent growth. When thinking about medication impacts on pregnancy, keep in mind the six teratology principles: genetic vulnerability, development stage, mechanisms, end points, access, and dosage response. An anatomical or structural defect evident at birth is known as a congenital malformation. Genetic causes, environmental stressors, or a mix of the two can induce congenital abnormalities during foetal development. The majority of congenital abnormalities have a threshold impact and are influenced by a mix of genetic and environmental variables. Teratogenic substances generally destroy the embryo rather than induce congenital abnormalities during the first two weeks of pregnancy. Major abnormalities are more prevalent in early embryos than in newborns, yet the majority of seriously damaged embryos spontaneously terminate during the first six to eight weeks of pregnancy. Teratogenic agents are more likely to induce significant congenital abnormalities between days 15 and 60 of organogenesis.

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