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A REVIEW ON TERATOGENICITY: MECHANISMS OF TERATOGENS AND RISK MANAGEMENT

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Abstract:

Teratogenicity is recognized as an important part of overall toxicology. The teratogenic risk factors are undetermined for more than 90% of drugs. The common teratogenic mechanism and effects are based on teratogenic compounds and several agents known as physical agents, chemical agents, and biological agents. Millions of different chemicals are exposed by humans and they show negative impacts by penetratinginto human tissues, developing fetuses, and the reproductive health of humans. The teratogenic mechanism in pregnancy shows its effects on the developing fetus and sometimes it leads to suppression of fetal growth. Itsignifies the structural malformations during fetal development. It is a process by which congenital birth defects occur due some biological infections, pharmacological drugs, industrial pollutants, and maternal health problems. Teratology is the science that investigates the congenital malformations and their causes.

Keywords: Teratogenicity, Human tissue, Management teratogens factors

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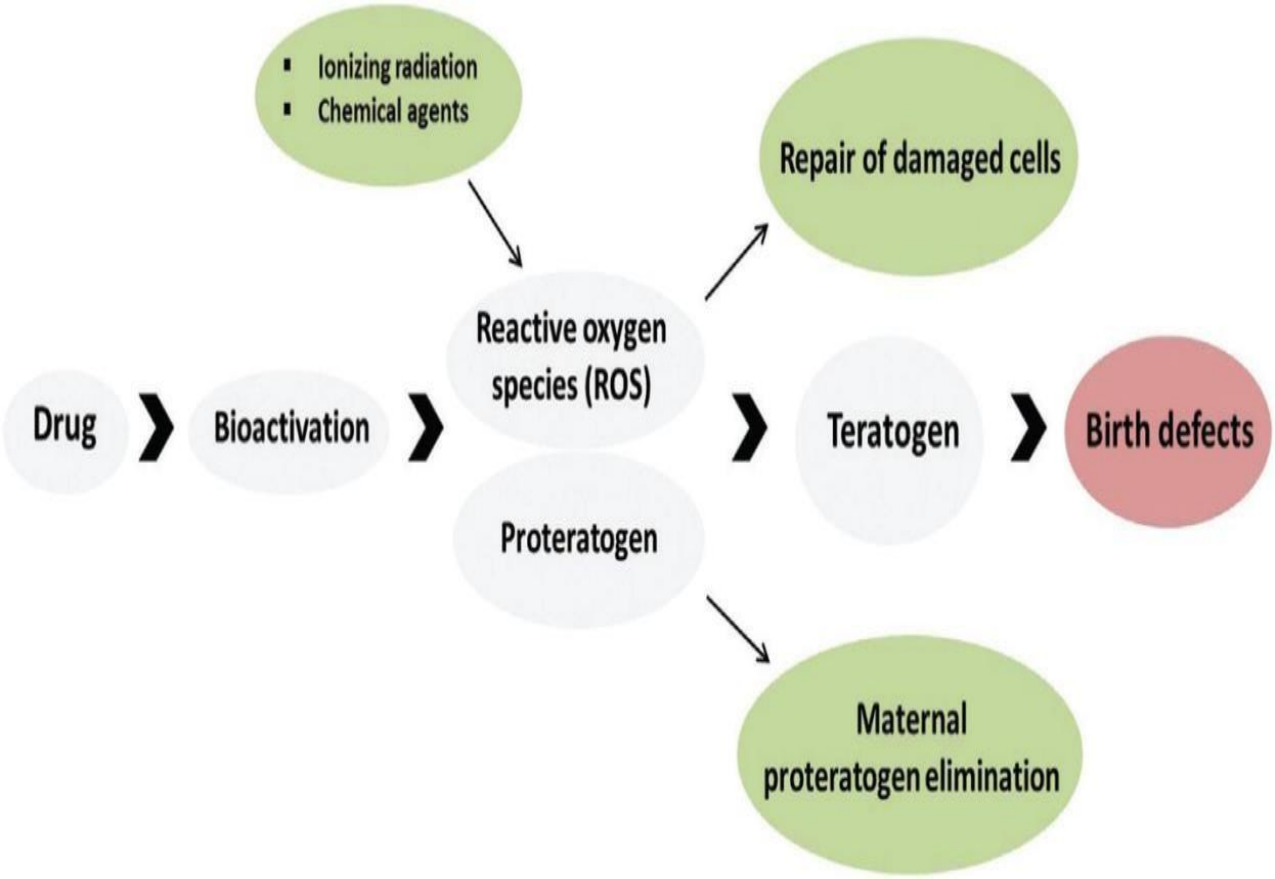
1. INTRODUCTION:

The term teratogen i s derived from the Greek word. Teras which means monster or marvel. They are environmental agents such as drugs, viruses, lack of nutrients, and physical or chemical elements. Teratogens generate permanent functional or morphological changes in the newborn. Exposure to teratogenic chemicals prior to conception during prenatal or postnatal development leads to manifestations of developmental toxicity including the death of the developing organism, structural abnormality, and functional deficiency. (Figure 1)

Figure 1: Action of Teratogenic agents



Teratogenicity signifies structural malformations during foetal development. They are responsible for causing congenital malformation. Birth defects are the leading cause of infant mortality and the etiological pathways are the leading cause by many different factors (e.g., genetics, environmental agents, medications, physical conditions) Maternal determinants, including drug administration, distribution, metabolism, and excretion may also play a crucial role [1].

2. HISTORY OF TERATOGENICITY

Teratogenicity is the science that studies the causes, mechanisms, and patterns of abnormal development. The first human with teratogen was identified in 1941 by an opthalmologist. Norman Gregg was a Maternal rubella infection in pregnancy, producing a triad of defects in the infants. Teratology asa modern science was first born in 1930. During the period of 1930 few experiments were conducted on pregnant pigs. The pigs had a deficiency of vitamin A and all these piglets suffered from malformations [2].

- In 1928: Exposure to therapeutic radiation during pregnancy led to a microcephalic baby.
- In 1933: A deficiency of vitamin A in 1st month before pregnancy and during pregnancy led to

anophthalmia.

➢ In 1941: A German measles (rubella) in pregnancy caused teratogenicity (blindness, deafness,mental retardation, death)

➢In 1944: Malformation due to nutritional deficiency.

2.1. TYPES OF TERATOGENS

- Physical agents
- Chemical agents
- Chemicals and drugs
- Metabolic conditions
- Industrial chemicals
- Radiation
- Genetic factors
- Alcohol
- Cigarettes
- Environmental agents
- Infectious agents

2.2. MECHANISM OF TERATOGENIC AGENTS

Mechanisms producing major structural birth defects associated with medications involve the following mechanisms

a. Folate antagonism

b. Neural crest disruption

c. Endocrine disruption

d. Oxidative stress

e. Vascular disruption

f. Specific receptor or enzyme-mediated teratogenesis

Some of these mechanisms are principally understood from animal models. These mechanismsmay produce birth defects in humans.

Some drugs may be involved in multiple mechanisms forproducing birth defects [3].

a. Folate Antagonism

Folate, the generic term for a water-soluble vitamin B, occurs in high concentrations in certain natural foods (fruits, leafy green vegetables, beans, spinach, and meat) as polyglutamate. The synthetic form of folic acid is taken in the form of medications as mono glutamic acid. Folic acid has a higher bioavailability than food folate. It is converted through two reduction reactions by dihydrofolate reductase (DHFR) to the naturally bioactive form of tetrahydrofolate (THF), which is converted into 5-methyl tetrahydrofolate (5-MTHF). 5- methyl tetrahydrofolate is the main form of folate in blood circulation and it is transported into cells by three routes known as membrane-associated receptors, Folate inside the cell, acts as an essential co-enzyme in many biological reactions by being an acceptor or donor of 1-carbon units. (Figure 2). For example: purine, pyrimidine synthesis, and DNA methylation reactions. Several drugs disturb the folate metabolism and may have a teratogenic effect through inhibition of thefolate methylation cycle. Two general groups of drugs act as a folate antagonists. The first group contains competitive inhibitors of DHFR and includes methotrexate, sulfasalazine, triamterene, and trimethoprim. They block the conversion of folate to THF by binding irreversibly to the enzyme. They are used in the treatment of a variety of diseases, such as inflammatory bowel diseases, rheumatoid arthritis, hypertension, and urinary tract infections. The second group of drugs may antagonize other enzymes in the folate metabolism, impair folate absorption or increase folate degradation. This group primarily consists of anti-epileptic drugs, including valproic acid, carbamazepine, and phenytoin. The teratogenicity of folate antagonists in humans was first suggested by the reports of women who were given aminopterin in their first trimester of pregnancy to induce abortion. Some anti-epileptic drugs, e.g.carbamazepine and valproic acid, are generally known to increase the risk of folate-sensitive birth defects, such as neural tube defects, orofacial clefts, and limb defects.

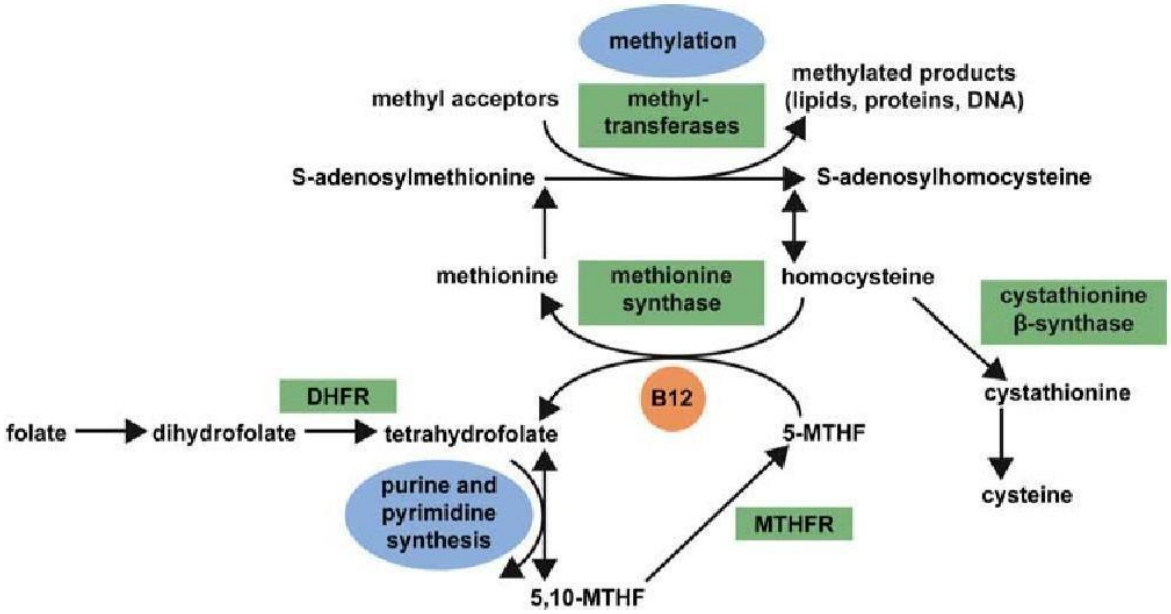


Figure 2: Mechanism of Tetrahydrofolate

Experimental studies in a number of animal species demonstrated that folate deficiency causes intrauterine death, growth retardation, and various congenital malformations. The fact that folic acid supplementation in the periconceptional period decreases the risk of neural tube defects in humans [4]. Recently, low blood folate status has been associated with an increased risk of neural tube defects. The exact mechanism by which disturbance of the folate metabolism increases the risk of neural tube defects is unclear. Women who carry a fetus with a neural tube de methyltransferases have significantly higher levels of homocysteine in plasma and amniotic fluid. First, homocysteine itself may be teratogenicity during the neurulation process, causing dysmorphogenesis of the neural tube, heart, and ventral wall in chick embryos. In rats and mouse embryos, however, increased homocysteine levels did not cause neuraltube defects. Therefore, it seems that elevated plasma homocysteine levels itself may not cause neural tube defects, but are a biomarker of disturbances in the methylation cycle which may result in neural tube defects. More likely, intracellular accumulation of homocysteine leads to increased levels of S-adenosyl homocysteine, which is a competitive inhibitor of many methyltransferases, through whichgene expression, protein function, and lipid and neurotransmitter metabolisms might be dysregulated. Furthermore, the decreased remethylation of homocysteine to methionine leads to decreased levels of S- S-adenosylmethionine, which is the most important methyl-group donor in themethylation cycle. As a result, neurulation could be disturbed by inadequate gene and amino acid methylation. Methylation steps also play an important role in the folate metabolism of liquids and neurotransmitters and in the detoxification of exogenous substances. This stress plays crucial role in folate metabolism for normal cellular function, especially during cell division and differentiation. This hypothesis is supported by previous studies showing that methionine is required for normal neural tubeclosure in rat embryos. Disturbances in folate metabolism are also thought to play a role in the etiologyof orofacial clefts, heart anomalies, limb, reduction defects, atresia, and urinary tract anomalies. Since folic acid supplement action alone or in multivitamins, seems to have a protective effect on the occurrence of birth defects.

Table 1: Drugs associated with folate antagonism

Medication	Main indication	Interference with folate metabolism
Phenobarbital	Epilepsy	Impairment of folateabsorption
Carbamazepine	Epilepsy, bipolardisorder	Impairment of folateabsorption
Cholestyramine	Hypercholesterolemia	Impairment of folateand vitamin B12 absorption
Cyclosporine	Transplants, psoriasis,atopic dermatitis	Possible interferencefolate-dependent remethylation
Methotrexate	Cancer, some autoimmune disease(rheumatoid arthritis, psoriasis)	Inhibition of DHFR
Metformin	Diabetes	Interference of vitamin B12
Nicotinic acid	Hypercholesterolemia	Decreases activity of CBS
Valproic acid	Epilepsy, migraine headache	Antimetabolite of folate
Primidone	Epilepsy	Impairment of folateabsorption
Trimethoprim	Urinary tract infection	Inhibition of DHFR
Sulfasalazine	Inflammatory bowel diseases, rheumatoid arthritis	Inhibition of DHFR
Pyrimethamine	Malaria	Inhibition of DHFR

b. Neural crest cell disruption

The neural crest is an important pluripotent cell population that originates in the neural folds. The neural crest can be divided into two major populations: the cranial and truncal neural crest. During neurulation, the Neural crest cells detach from the Neural folds and migrate into the embryo to give riseto numerous structures. In the craniofacial region, various cell types and structures, including intramembranous bone, cartilage, nerves, and muscles are derived from the cranial neural crest. The truncal Neural crest produces important components of the peripheral nervous system. The cardiac neural crest is a subpopulation of the cranial neural crest, which migrates into the cardiac outflow tract to medicine separation and into other derivatives of the pharyngeal arches, such as the thymus and thethyroid and parathyroid glands. Therefore, neural crest-related cardiovascular malformations include aortic arch anomalies and conotruncal defects [5].

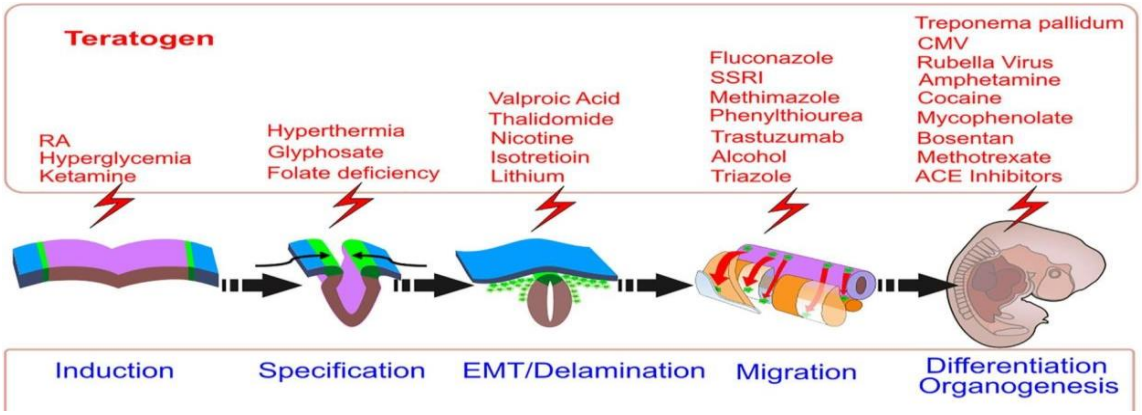


Figure 3: The role of Teratogens in neural crest development

Proper induction, migration, proliferation, and differentiation of neural crest cells are tightly regulated. Avariety of molecular signals and receptors are implicated in neural crest cell development. Fibroblast growth factors may be involved in the induction of neural crest cells. Integrins, a family of cell surface receptors, play a role in the interaction of neural crest cells with the extracellular matrix, whereas interactions between neural crest cells are mediated by cadherins. Endothelial and their receptors are required for the mitigation, differentiation, and proliferation of neural crest cells. Therefore, drugs thatinterfere with these molecular pathways, such as bosentan, which is indicated for THE treatment of pulmonary hypertension and to reduce new digital ulcers associated with system sclerosis, may induce neural crest-related malformations. In addition, in vivo and in vitro experiments suggested that altering levels of folate and homocysteine cause abnormalities of cardiac neural crest cell migration, differentiation, and cell cycle progression, thereby connecting this teratogenic mechanism with folate antagonism. However, one of the most important signalling molecules in neural crest cell development isretinoic acid, the biologically active form of vitamin A. Excess or shortage of retinoic acid seems to causeneural crest-related malformations, indicating that proper retinoid acid synthesis and degradation are performed by retinal dehydrogenases and CYP26. In addition to retinoids used in the treatment of dermatological conditions, such as tretinoin, isotretinoin, and etretinate, other drugs that inhibit these enzymes may also be involved in disturbances of retinoid homeostasis [6].

c. Endocrine Disruption: Sex Hormones

Since the 1940s, a number of drugs have been developed to inhibit the actions of hormones including diethylstilbestrol (DES), oral contraceptives, and hormones used in fertility treatment. These medications and other endocrine-disrupting chemicals (EDCS), such as bisphenol A and phthalates, may interfere with the physiologic functions of endogenous hormones by affecting their release, binding, or metabolism. Their actions may not only depend upon their affinity or specificity for the estrogens and androgen receptors but also upon their ability to activate or inhibit receptor-mediated actions, which are dependent upon the absorption, distribution, metabolism, and excretion (ADME) of these molecules as well. The actions of EDCs in utero have been of concern because of their possible impact on the developing reproductive systems, especially since the treatment of pregnant women with the synthetic estrogen DES led to an increased risk of vaginal adenocarcinoma. Since human effects were identified first, animal studies have been conducted to confirm these clinical observations and to investigate the differences between synthetic and natural estrogen actions on the embryo or foetus. It is well known that human sex hormone-binding globulin has a substantially higher affinity for estradiol than for DES or other synthetic hormones, which covalently bind which suggests that DES may be more readily availableto cross the placenta. DES also metabolizes to reactive intermediates which covalently bind, whereasestradiol is not metabolized to similar reactive intermediates which covalently bind, whereas estradiol is not metabolized to similar reactive intermediates. In addition to drugs that influence endocrine homeostasis as their primary mechanism of action, coatings for oral medications, such as mesalamine and omeprazole, maybe a source of EDC exposure. These enteric coatings contain phthalates, which may affect human male reproductive development due to their anti-androgenic properties. Additionallyother preparations may contain phthalates as plasticizers, but it should be noted that phthalates do not bio-accumulate and are excreted rapidly in contrast to some other EDCs.

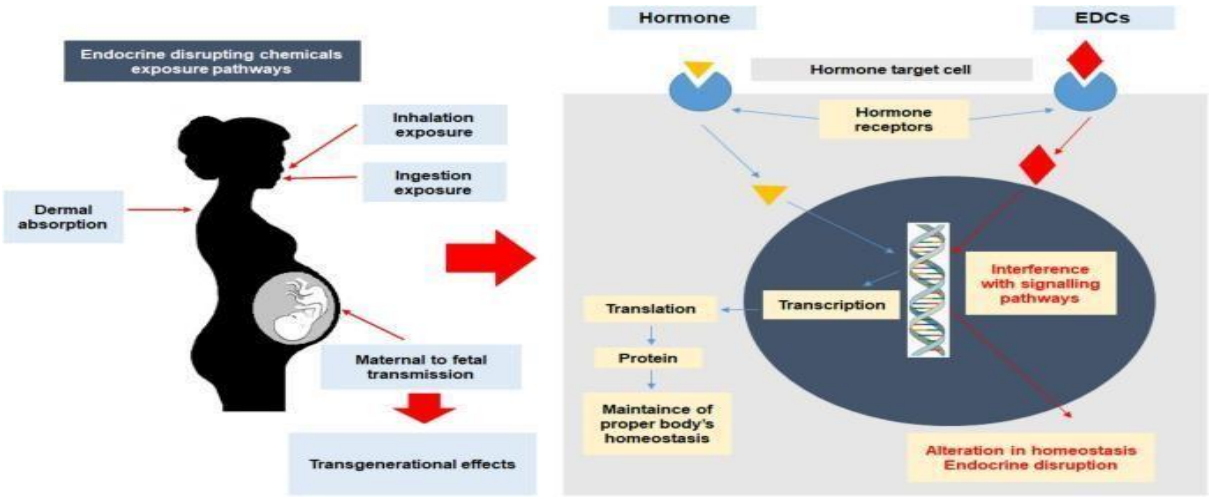


Figure 4: Endocrine disruptors driven by Female reproductive ailment.

Since synthetic hormones and EDCs may affect endocrine homeostasis in multiple ways, the underlyingteratogenic mechanisms are often difficult. Male sexual differentiation generally depends on a balanced androgen/estrogen ratio. In mice, estrogens impair fetal Leydig cell development, and as a consequence, testosterone production is decreased. Phthalates that induce male reproductive disorders in rats mainly do so through Inhibition of steroidogenesis by the foetal testis, but This does not occur in vitrowith human fetal Leydig cells. Testosterone secretion is responsible for most of the masculinization process, including the development of the male reproductive tract and external genitalia. In addition, estrogen exposure also suppresses the production of insulin-like factors 3 by fetal Leydig cells. Inhumans, a deficiency in androgen production or action seems more important than estrogen exposure in the etiology of cryotorchidism, since the inhibitory effects of estrogens on testicular steroidogenesis and testicular descent are only mediated through estrogen receptors in mice, which isnot present in human fetal testes [7].

Alternative mechanisms by which EDCs could cause male reproductive disorders have also been suggested. These mechanisms include disruption of the androgen signaling pathway (e.g. suppression of androgen receptor expression), resistance to anti–Mullerian hormones (AMH), and inhibition ofenzymes involved in the inactivation of sex steroids. However, the involvement of these mechanisms in endocrine disruption seems U likely for various reasons. Although it has been shown that foetal exposure to Chemicals that alter the androgen signalling pathway can induce hypospadias and cryotorchidism in ry as, the dose needed to induce these effects is very high, which makes this mode for EDC induced teratogenesis doubtful.

d. Oxidative stress

In vivo, several drugs known as redox cycling agents and used in the treatment of epilepsy, cardiac arrhythmias, and cancer undergo single electron reduction reactions yielding radical species. In radical cycling reactions that involve oxygen reactive oxygen species (ROS), such as hydrogen oxide, alkyl peroxides, and various radicals (e.g., hydroxyl and superoxide) are generated. The creation of ROS can be decreased or reversed by various enzymes, e.g., superoxide dismutase, catalase and glutathione reductase, and by antioxidants. Endogenous ROS can also be harmful by binding covalently or irreversiblyto cellular macromolecules. Oxidative stress, an imbalance between ROS generation and antioxidant defence mechanisms of a cell or tissues, causes irreversible oxidation of DNA, proteins, and lipids leading to the inactivation of many enzymes and cell death. In addition to damaging cellular macromolecules, oxidative stress may affect gene expression by interfering with the activity of redox-sensitive transcription factors and sign la transduction by oxidizing stress may affect gene expression by interfering with the activity of redox-sensitive transcription factors and signal transduction by oxidizing thiols.

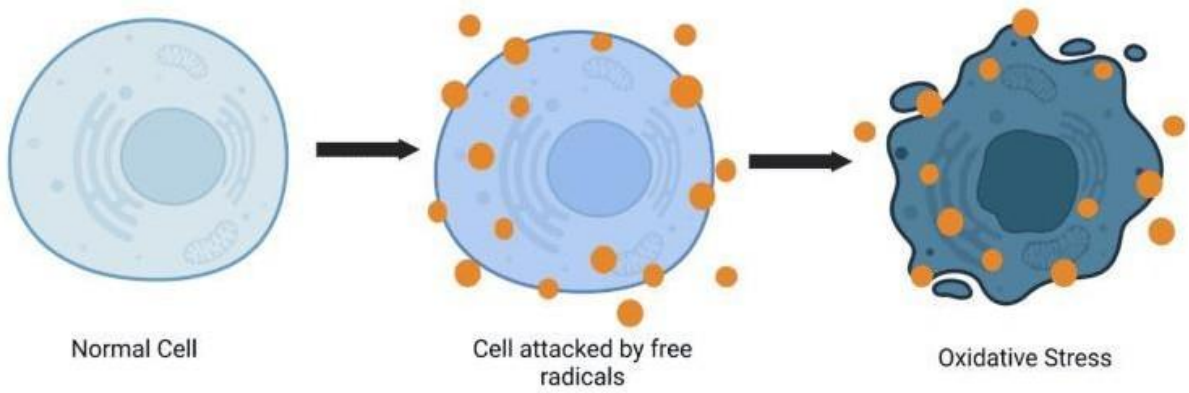


Figure 5: Molecular and biochemical determinants of Oxidative stress teratogenesis.

During the prenatal period, this may result in birth defects and growth retardation, and in severe cases in-utero death. The developing embryo is especially susceptible to high levels of ROS because of its weak antioxidant defence, in particular in the early stages of organogenesis, although placental enzymes play a role in protecting the foetus against oxidative stress. Oxidative stress is postulated to be involved in the pathogenesis of a wide spectrum of birth defects including skeletal malformations, limb defects, Neural tube defects, and cardiovascular defects. Several drugs are known to induce Oxidative stress, which is suspected to be their main teratogenic mechanism. Among these drugs are thalidomide, phenytoin, valproic acid, class lll antiarrhythmic drugs, iron supplements, and various chemotherapeutic drugs [8].

However, it is important to notice that ROS are intermediary compounds with unpaired electrons and asa consequence, have a very short lifetime ranging from nanoseconds to milliseconds. Therefore, ROS are generally unstable to be transferred from the mother to the developing embryo or foetus. Whenever ROS are increased in embryos, in the result of embryonic metabolic changes rather than exposure to ROS of maternal origin. Increased in embryonic ROS may be caused by increased enzymatic bioactivation of pro teratogens, including bioactivation of the drugs. The peroxidase component can bio-activate exogenous substances, including phenytoin, and related Teratogens to toxic reactive intermediates that initiate ROS formation. There is evidence that lipoxygenase (LPOs) oxidize proteratogens yielding free radical intermediates substantially expressed in embryonic tissues. As a result, it is assumed that the bio-activation of pro teratogens by embryonic pHSs and LPOs is necessary for the formation of ROS and subsequent macro molecule damage in the developing embryo.

e. Vascular Disruption

Vascular disruption defects are structural birth defects resulting from interference with the extrinsic breakdown of originally normal prenatal development of the arteries, veins, and capillaries.

Traditionally, it has been stressed that a teratogen exerts its influence on the foetus during the first 3 monthsof development. Prenatal Exposure to agents which can induce vascular disruption, however, can also induce damage later in pregnancy to structures that were initially formed normally. After birth, it may beimpossible to determine whether a certain structural abnormality, such as limb defects, is the result of an intrinsically abnormal developmental process, vascular disturbances. vascular disruption refers to a disturbance in the blood circulation in the uterine placental unit, the placental foetal unit or the foetus itself. These disturbances include hyoerperfusion,hypoxia, and obstruction. They may be caused by acute or chronic diseases in uterine blood flow, vascular infections, or an abnormal anatomy in the uterine placental unit. Factors such as placental insufficiency, amnion rupture and umbilical cord obstruction may cause failures in the vascular supply in the placental fetal unit. In the foetus, disruptionof newly formed vessels, external compression, embolic events, premature regression of embryonic vessels, and occlusion. Vasoconstriction of maternal and foetal vessels, hypoperfusion and obstruction cause a reduced supply of nutrients to THE embryonic tissues, which can affect the development and growth of embryonic structures or result in tissue loss [14,15].

Exposure to vasoactive substances in pregnancy, especially to those with vasoconstrictive effects, has been hypothesized to play a causal role in vascular

disruption defects. These teratogens could decrease placental or foetal blood flow or affect the development of blood vessels, thereby changing the structure/anatomy of the vasculature. Therefore, the majority of defects caused by tissue damage through vascular disruption occur in structures supplied by the most peripheral vasculature, such as the distal limbs and the embryonic intestine. Birth defects that were attributed to vascular disruption includeterminal limb reductions, porencephaly, gastroschisis, and small intestinal atresia. However, there are no known experimental models for the complete range of birth defects caused by vascular disruption. Themajority of evidence in support of this mechanism comes from case reports with suspected vascular events such as occlusion, embolic, amnion rupture, and twin placental vessel anastomoses.

f. Specific Receptors or Enzyme – mediated Teratogenesis

Many Medical drugs act on a Specific receptor or enzyme in the body, leading to a particular mechanism of action. Below we describe the possible effects of inhibition or stimulation of some of these specific receptors and enzymes on foetal development.

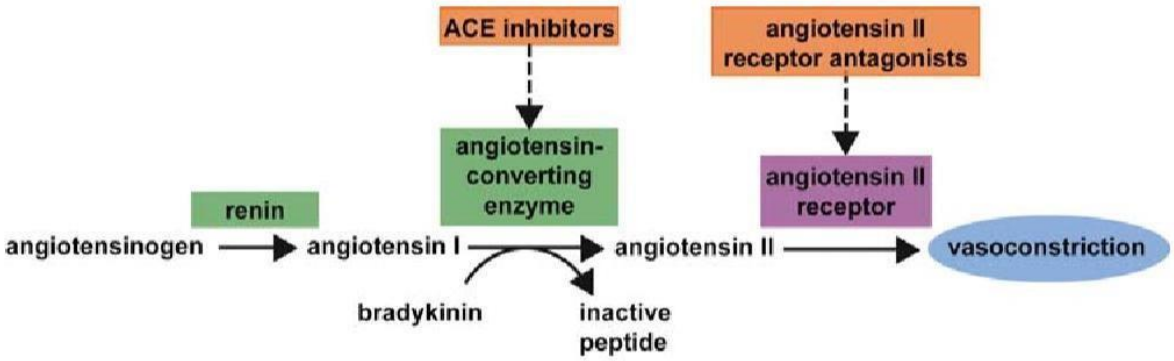


Figure 6: The renin-angiotensin system ACE, Angiotensin – converting enzyme.

- Angiotensin - converting enzyme and angiotensin ll receptors
- Hydroxymethylglutaryl - coenzyme A reductase
- Cyclooxygenase-l
- 5 - Methyl D – aspartate receptors
- 5 – Hydroxytryptamine receptors
- Alpha – Aminobutyric acid receptors
- Carbonic anhydrase

3. DIAGNOSIS OF TERATOGENS

Due to the number of new substances coming into use every year and the increasing amounts of chemicals, that are introduced into the environment, there is a high demand for a rapid, reliable, andcost–effective method for the detection of developmental toxicity. To meet this challenge various in vitro techniques have been established in additional to in vivo animal testing. During pregnancy, prenatal testingcould be done for determination of teratogens and the growth of foetus [10,11]

3.1. Screening Tests

i. Whole embryo culture test
ii. Micro mass teratogenic test
iii. Embryonic stem cells test
iv. Dictyostelium discoideum-based assay

i. Whole Embryo Culture Test:

A screening test is a procedure or test is done to see if a woman or her baby might have certain problems. A screening test does not provide a Specific diagnosis that requires a diagnostic test. A screening test can sometimes give an abnormal result even when there is nothing wrong with the mother or her baby. This screen includes a maternal blood test and an ultrasound screening during thefirst trimester U silly consists of blood tests to measure levels of pregnancy-associated placental protein A and beta–human chorionic gonadotropin in the pregnant woman's blood. Ultrasonography to measure a fluid-filled space near the back of the foetus neck. Ultrasonography can help to estimate the risk of Down syndrome and certain other chromosomal abnormalities. It can show whether the space atthe back of the foetus neck is enlarged. This test can accurately determine the risk of Down syndrome and some other chromosomal abnormalities

in couples with a high risk of having a foetus with a chromosomal abnormality. The test can be done as early as 10 weeks of pregnancy but can also be done later.

ii. Micro mass teratogenic Test

The *in vitro* Micro mass teratogen test is intended to identify those Chemical substances which can induce malformations resulting in embryotoxicity. The test can be employed on a number of compoundssuch as pharmaceuticals, agriculture, industrial chemicals, consumer products, contaminants, and food additives. It can detect various test agents that interfere with some of the normal processes of cell differentiation observed in the developing embryo resulting in embryo toxicity.

iii. Embryonic stem cells Test

Stem cells in the body have a unique ability to renew themselves and give rise to more specialized cell types having functional commitments. Under specified growth conditions, these cell types remain U-specialized but can be triggered to become specific cell types of the body such as heart, nerve, skim cells. This ability of embryonic stem cells for directed differentiation makes it a prominent candidate as a screening tool in revealing safer and better drugs. In addition, genetic variations and birth defects causedby mutations and teratogens affecting early human development could also be studied on this basis.

Moreover, the replacement of animal testing is needed because it involves ethical, legal, and cost issues. Thus, there is a strong requirement for validated and reliable, if achievable, human stem cells based on developmental assays for pharmacological and toxicological screening.

4. RISK MANAGEMENT

A teratogen is a substance that can adversely affect the development of an embryo or a fetus if administered under Specific conditions of dose, route of administration, gestational age, and genotype. To minimize foetal harm when prescribing potential teratogen, risk management programs have also been developed for certain medications. The development and implementation of teratogenic risk management programs should also take into consideration of patients' experience of using a Medication [12,13,16].

4.1. Risk minimization measure

- Teratogenicity counseling
- Contraceptive counseling
- Pregnancy testing before or at the start of treatment
- Pregnancy testing during treatment
- Use of contraception before or on starting treatment
- Use of contraception during treatment

Table 2: Teratogenic Drugs and Agents

Medicine/chemical class	Effects	Recommendations
ACE (angiotensin converting enzyme inhibitors) - Captopril, enalapril, fosinopril sodium, lisinopril + hydrochlorothiazide, ramipril	Second and Third trimester exposure toACE inhibitors are associated with oligohydraminos, hypocalvaria, anuria, renal failure, neonatal hypotension, and patent ductus arteriosus	Avoid in the second and third trimester.
Alcohol - Alcohol	Mental retardation, intra uterine, growth retardation, small head, foetal alcohol,syndrome characterised by maxillary hypoplasia,congenital heart disease.	Do not use during pregnancy.

Androgenic agents - Ethisterone,testosterone, norethisterone	Ambiguous externalgenitalia, masculinization offemale foetus especially in 1st trimester.	Avoid prior to pregnancy and during pregnancy especially during the first trimester.
Antibiotics - Tetracycline	Yellow staining of teeth and diminished growth of the longbones.	Avoid during second and third trimester.
Antibiotics - Nitrofurantoin	Haemolytic effects ofthe new born when used in the last trimester.	Avoid during pregnancy.
Antibiotics - Streptomycin	Readily crosses the placenta and it shouldbe used with caution to prevent ototoxicity in the foetus.	Avoid during thesecond and thirdtrimester.
Anti – coagulants - Warfarin	Crosses the placenta and causes bleeding in the foetus resulting into spontaneous abortion, stillbirth, neonatal death, andpreterm birth. Cause birth defects like mental retardation, blindness etc.	Avoid during pregnancy especially in the first and thirdtrimester.
Anticonvulsants - Phenytoin, valproic acid, carbamazepine, phenobarbital,lamotrigine	Phenytoin causesfoetal hydantoin syndrome consisting ofintrauterine growth retardation, microcephaly, mentalretardation. Carbamazepine causes neural tube defects, other abnormalities. Valproic acid causes spinal bifida and otherneural tube defects.	Avoid during pregnancy women of child bearing age who are using these medications should be given contraceptive advice. Women who wish to get pregnant while on this medication should be referred to a gynaecologist for specialist management.
Antifungal - Fluconazole	Congenital abnormalities when used in first trimesterat high doses e.g. malformed bones, face, head, heart.	Avoid during pregnancy
Antidepressant - Lithium	Various malformations including cardiac abnormalities.	Avoid during first trimester, if used during pregnancyserum lithium concentration monitoring is advised to avoid toxicity in the neonate.
Chemotherapeutic agents	Stunted growth, cleft palate.	Avoid during pregnancy.
Folic antagonist - Methotrexate	Multiple malformations	Avoid during pregnancy. Use contraceptives during treatment and for at least 3 months after treatment in both men and women.
Lipid-lowering - Statins	Congenital anomalies, including vertebral, anal, cardiac, tracheal, oesophageal, renal and limb deficiency and	Avoid during pregnancy. Adequate contraceptive is

	intrauterine growth retardation (IUGR) especially ifused in the first trimester	required during treatment and for 1 month after treatment.
Prostaglandin analogues - Misoprostol	Potent uterine stimulant and has teratogenic risk whentaken in the first trimester.	Avoid during pregnancy.
Nicotine	Intrauterine growth restriction. Prematuredelivery. Nicotine constricts uterine blood flow thus reducing oxygen 16 supply and nutrientsto the growing babyaffecting mental development.	Avoid during pregnancy.
NSAIDs - Naproxen, celecoxib, acetylsalicylic acid, diclofenac, Ibuprofen, Indomethacin	Ibuprofen, naproxen,diclofenac and celecoxib increases therisk of miscarriage in the first half of pregnancy cause ablood vessel in thefoetus to close prematurely and persistent pulmonaryhypertension of the new born.	Avoid during pregnancy especially in the third trimester.
Opioids - Oxycodone, morphine,codeine, hydrocodoneand hydromorphone.	Birth defects of thebrain, spine. Respiratory depressionand withdrawal symptoms can occur inthe neonate if opioid used during delivery.	Avoid during pregnancy.
Ionising Radiation	Chromosome injury	Avoid during pregnancy
Tranquilisers - Thalidomide	Limb abnormalities including absence of limbs, abnormally shortened limbs, absence of external ears, congenital heartdisease etc.	Do not use during pregnancy. Use Effective contraceptives 1 month before and one month after use. Men should use condoms during treatment and at least 2 week after stopping.
Vitamin A - Retinoic acid e.g. isotretinoin	Very teratogenic evenat doses. Cleft palate,neural tube defects, thymus aplasia etc.	Avoid during pregnancy.

5. CONCLUSION:

Most pregnancies are not diagnosed until after the early period of organogenesis. Environmental exposures, illness and teratogen can have adverse effects on the growth of foetus in the early stage of pregnancy. Chronic disease management and modification of lifestyle behaviours can be adjusted prior to contraception. Precontraception care could protect from these adverse effects by informing, screening. Keeping the foetus safe from teratogens during pregnancy can help to prevent congenital disabilities. The first step is to be aware that certain harmful substances can reach the foetus in the womb and negatively affect the development of organs. Avoiding teratogen helps in supporting a healthy pregnancy and gives the baby great health. Patient must be open with the healthcare provider about their Medication as well as alcohol consumption and workplace or living conditions.

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